Challenges in Rhinology

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ISBN 978-3-030-50898-2 ISBN 978-3-030-50899-9 (eBook)
https://doi.org/10.1007/978-3-030-50899-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The inspiration for this book occurred when three of the editors (RM, CC, and myself) were floating on a gulet off the coast near Marmaris. After dinner, discussions turned to unsolved questions which we had asked ourselves over the years about Rhinology, our special subject. We realized that no one had put the answers to, or their pet theories about, these questions into a book—yet such a volume would be of use to many young Rhinologists, and even to their elders and to those in other related fields. Hence, the current volume.

Its gestation is also of interest since the initial version of most chapters has been researched and written by a young and enthusiastic specialist. This was then scrutinized and altered by one of his or her local mentors before being sent to a recognized expert in the field. Finally, I have read them all and made a few of my own suggestions, largely related to my own experience, or an update from recent papers.

The resulting volume has 49 chapters, written by over 100 authors from 21 countries—so it holds a widespread knowledge and expertise. The subjects range from basic anatomy and physiology, such as the importance of extra sinuses and the nasal cycle, through pathology: epistaxis, hyperreactivity, cerebrospinal fluid rhinorrhoea, rhinitis, and rhinosinusitis of all kinds, immune deficiency, to therapy: both medical and surgical.

Budding rhinoplasty surgeons will find plenty to occupy them: Chapters 22–29 concern this fascinating subject and show how the practice has evolved in recent years. Those who use medical treatments have multiple chapters concerning allergic rhinitis, local allergic rhinitis, paediatric rhinitis, chronic rhinosinusitis with and without nasal polyps. Therapies such as aspirin desensitization, combination sprays, complementary medicine, anti-fungals, allergen-specific immunotherapy, and biologics are included.

There are chapters suited for ear specialists, such as the significance of rhinitis in otitis media with effusion or whether the perforated eardrum is analogous to an accessory sinus ostium. Those who treat cough have Chaps. 42 and 44. Lower airways are also included in Chaps. 40 and 41, where the concept of united airways is explored and whether treating rhinitis helps asthma is discussed. Chapter 33 is devoted to optimal anaesthesia for nasal surgery, and the final chapter concerns forensic aspects of Rhinology.

Our hope is that this book will act as a wise elder to whom the Rhinologist can turn for answers to many of their questions. If there are some with which we have failed to deal, please let us know.

London, UK
April 1, 2020

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Is the Nasal Cycle Real? How Important Is It?

1

Nihat Susaman, Cemal Cingi, and Joaquim Mullol

1.1 Nasal Physiology

The nose plays an essential physiological role in how the upper airway functions, by heating and adding moisture to the inhaled air. Adults are thought to breathe in up to 10,000 L of air in any 24-h period [1]. The lumen of the nose is the first point at which particles inhaled from the environment are trapped. The nasal hairs trap the biggest particles. The resistance to airflow of the airway as a whole is influenced by resistance offered by the nose; indeed, almost half the resistance in adults comes from the nasal cavity [1–4]. The mucosal surfaces of the nose exchange heat so as to preserve the temperature of the air in the nose at between 31 and 37 °C [1].

It has been theorised that the position occupied by the sphenopalatine artery is key to understanding how efficiently heat is exchanged in the nose. This artery passes over the turbinates in an anterior direction, whilst inhaled air moves backwards, and this allows a countercurrent mechanism to exchange heat between air and blood [1]. This countercurrent leads to greater efficiency of heat transfer, albeit

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_1

the mechanism has a degree of imperfection inherent in it, and up to 10% of heat loss is due to this nasal mechanism.

A further key role played by the nose is the addition of moisture to inhaled air [1]. The mucosa is richly vascularised, and air is already at 95% relative humidity when it reaches the nasopharynx. Mucociliary flow depends on nasal secretions and functioning cilia, and this then contributes to the immune functions of the nose. Additionally, several reflexes of neurovascular type affect nasal function. Pressure applied to the lateral nasal wall on one side produces pulmonary congestion ipsilaterally via the nasopulmonary reflex, for example [1, 5].

The nose possibly also modifies vocal production. A number of authors have suggested a role for nasal airflow in how high-frequency sounds, including consonants, are produced [1]. The way air flows through the nose also helps olfaction to occur. Sniffing is an action enabling inhaled particles to come into contact with the olfactory mucosa situated near the basal aspect of the skull [1].

For the sinuses and nose to function normally, ciliary flow must be normal. There are two layers that comprise the nose's clearance mechanism which plays a key role in defence. The pseudostratified mucosa covers the entire nose and paranasal sinuses and is the site of mucociliary flow [6].

1.2 Normal Nasal Reflexes

A widespread network of nerves supplies the nose. Many different reflexes are responsible for the cyclic alteration in nasal congestion, discharge from the nose and sneezing. Whilst normally individuals do not notice such reflexes in action, they may sometimes alarm patients [7, 8]. Knowing how the nose's reflexes operate helps to separate normal from diseased responses. Those reflexes considered physiological include [9–11]:

- Postural reflexes—lying supine causes greater nasal congestion, and if an individual is lying on one side, the ipsilateral nasal cavity becomes more congested. When upright, there is a cyclical alternation of congestion, first, in one nostril and then the other.
- Crutch reflex, whereby pressure on the axilla produces nasal congestion on the same side.
- The reflex response to very high or low cutaneous temperatures is to induce sneezing.
- The reflex response to intense light in the visible or infrared range of the spectrum is to induce sneezing.
- The bronchonasal reflex activates constriction of the bronchi when the nose is stimulated, as occurs when inhaling cold air.
- Ovulatory rhinitis refers to greater congestion in the nose around the time of ovulation in females.

Some people sneeze in response to a range of stimuli. It is unclear how common such responses are, which renders their categorisation as physiological a complex issue, even though they do occur in the absence of other signs of ill-health [11].

- A genetic predisposition to sneeze following eating has been described, with gastric fullness as a putative mechanism whereby this occurs [12, 13].
- It has also been reported that erotic thoughts or the aftermath of orgasm may trigger sneezing.

1.3 Nasal Cycle

Normally the nose has a cyclical pattern in its physiology—the nasal cycle. The turbinates swell on alternate sides with a periodicity of 3 h, resulting in alternating blockage of one side of the nose [14]. White et al. [15] modelled the nasal cycle in silico and found that the side that remains patent tends to lose moisture from the mucosal surface through the process of heating and humidifying the inhaled air, whereas the blocked side has sufficient moisture content for mucociliary clearance to operate on a continual basis.

A certain group of individuals find that the nasal erectile tissues become engorged with blood for a period, followed by a return to the relaxed state [16, 17]. The exact number of individuals thus affected is estimated to range from 20–40% [18–20] to more than 80% [16, 18, 21, 22]. In such cases, the turbinates swell on one side ('congested' state), resulting in blocked airflow, whilst the other side remains unswollen ('patent' state). The term 'nasal cycle' identifies this situation of obstruction or patency occurring with a periodicity of between 1 and 7 h [23]. The periodicity of the nasal cycle is composed of separate ultradian intervals lasting between 1 and 1.5 h [21]. Individuals usually fail to notice the phenomenon due to the fact that total resistance to the flow of air through the nose does not alter perceptibly [15, 24, 25].

Thus, air flows through the nasal cavity in an asymmetrical fashion, with the unblocked side allowing most of the air movement. Which side is dominant alternates every few hours or so [26–28]. When infections occur, the asymmetry is more marked, with the congested side becoming totally occluded and all air passing via the other side [29, 30]. Thus, this 'nasal cycle' can also be viewed as a matter of spontaneously occurring alternating lateralisation in resistance to airflow [31].

Eccles argues that F_{min} (a measure of the lowest flow of air on one side) has greater value in the assessment of how severely the nose is blocked than simply assessing the total resistance to airflow within the nose as a whole [32].

One side of the nose is always predominant in terms of airflow whilst the nasal cycle operates [30, 31]. However, there may not be a pattern of co-ordinated alternation between the two sides, and it is possible for an individual to have a nasal cycle where the two sides operate out of phase (completely or partially) with each other.

If a patient has a nose infection, they may feel as if both sides of the nose are blocked at the same time, a feeling accentuated by septal deviation. Nonetheless, neither Eccles et al. [30] nor Bende et al. [29] found objective evidence to confirm this in their research.

Kayser [33] was amongst the first to study the nasal cycle, publishing findings in 1895 related to nasal resistance to airflow. The method was to pass a known volume of air through the nose via the mouth as quickly as possible and thereby calculate the maximal flow rate. Whilst the resistance offered by the nose as a whole remained uniform, the left and right nasal passages varied in their resistance to a marked extent. Kayser was able to conclude from this that the resistance to airflow of the separate passages varies perpetually in an episodic fashion [33]. These alterations in level of occlusion in each side of the nose (and, hence, the existence of the nasal cycle) have been confirmed by many later researchers [26–28, 34–40]. 'Nasal cycle' may constitute a misnomer, given that the alternating levels of occlusion of each nasal passage seldom exhibit true periodicity [36], and regularity of the cycle is not a feature for which much evidence exists [37, 39, 41].

1.4 Mechanisms for the Nasal Cycle

The nose is the only part of the respiratory tract to feature lateralised alternation in airflow of several hours' duration, in other words the 'nasal cycle' [42–45]. A popular way to visualise the situation is as the volumes of the two nasal passages being inversely correlated [46]. There are vascular spaces underlying the septum and the turbinates that become alternately congested and decongested, leading to airflow alterations [26]. This venous congestion is under vascular sympathetic control [3, 47–49].

The variation in resistance to airflow is thus regulated by the autonomic innervation of the mucosal vasculature [31].

The classical way to view the nasal cycle is as a fluctuating state in which nasal airflow is restricted first on one side and then the other. The brainstem contains the ganglia responsible for the cycle. Within this model, the two sides spend equal periods being dominant for airflow, and the degree to which occlusion occurs should be the same regardless of the side undergoing congestion, so that airflow as a whole does not significantly alter. Of healthy individuals, 75% apparently exhibit the classical nasal cycle [50].

Experimental studies conducted on anaesthetised cats have demonstrated that electrical stimuli applied to the vasomotor centres in the medulla oblongata reproduce the pattern of alternating nasal airflow resistance through activating the blood supply to the nose, which is thought to occur in humans, too [51]. Control may also depend on hypothalamic centres involved with sympathetic nasal innervation [52]. Research using EEG (electroencephalogram) monitoring of the cortex indicated that the hemisphere that dominated cortical activity was contralateral to the nasal passage that had greatest patency at the time of recording [3, 53].

Mirza et al. [54] examined the effect of age on the pattern of rhythmic alternation in airflow resistance linked to activity in the nasal cycle. They report being the first researchers to do so. Their findings suggest that activity of the cycle decreases with advancing age.

Stoksted and Thomsen were able in 1953 to induce severe nasal congestion when the stellate ganglion of that side was blocked, with slight congestion of the other side [49]. Later, in 1981, and using the pig as animal model, Eccles and Eccles demonstrated how stimulating the sympathetic chain in the cervical region made blood vessels constrict ipsilaterally with a somewhat diminished (only about 5–10% of the ipsilateral effect) effect contralaterally [55]. It has been shown in cats that stimulating the brainstem unilaterally leads to vasoconstriction in the nose on the same side and vasodilation on the other side [51], a result which implies that there are central mechanisms at work in orchestrating the alternating changes in airflow that constitute the nasal cycle [3].

The fact that the nasal cycle-associated congestion reduces as people age may be attributable to loss of elasticity in the vasculature, mucosal ageing or alterations in sympathetic portions of the peripheral nervous system, including receptor changes [56]. However, if it is granted that the blood supply of the nose remains responsive to sympathetic innervation, in however reduced a way, the central nervous system must still be responsible overall; hence, changes in the CNS are ultimately responsible for the changes associated with ageing [3].

1.4.1 Autonomic Control of Nasal Venous Sinusoids

Venous sinusoids that lie beneath the mucosal surface of the nose are the site at which congestion and decongestion occur, leading to airflow alterations. The venous sinusoids act like erectile structures in the body. The front portion of the septum and the lower turbinates of the nose have especially abundant spongy tissue filled with venous sinusoids [57–59].

These sinusoids are richly innervated by adrenergic fibres of the sympathetic nervous system. It is evident that sympathetic innervation governs how congestion, and hence airflow resistance, occurs. Stimulating the sympathetic chain in the cervical region with a current leads to severe constriction of the vessels in the nose and a more patent nasal airway [47, 60–66]. The periodic alterations occurring in a reciprocal fashion that alter airflow through the nose, i.e. the nasal cycle, have been shown in the literature to cease functioning if the cervical sympathetic supply is disrupted or the stellate ganglion blocked [31, 47, 67–69].

1.5 Importance

The importance of the nasal cycle is suggested by its persistence during evolution [70]. It probably acts to allow one side of the nose to recover from exposure to drying air, pollution, etc., whilst the other side is functioning more. However, it is not

vital, since some 20–80% of studied populations lack a nasal cycle. The importance to rhinologists is firstly to remember it when examining or measuring the nose and not to immediately attribute unilateral obstruction to anatomical issues and secondly to ensure that nasal challenges, such as those with allergen or aspirin, are undertaken bilaterally.

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Are There Additional Nasal Sinuses? Do They Matter?

2

Ranko Mladina

2.1 Introduction

Krmpotić stated that the perpendicular plate of the ethmoidal bone as a great part of the nasal septal skeleton may be pneumatized, thus forming a cavity within this bony plate. This cavity was called *sinus septi nasi* (SSN) [1]. Unfortunately, everything stopped at this level: no data on sinus septi nasi and its possible diseases have been offered in the literature for decades, most probably since for a long time there was no possibility of CT scanning of the paranasal sinuses. At the same time, classic sinus X-rays of Waters' projection, as well as so-called tomographs, were the golden standard in the radiological diagnosis of the paranasal sinuses, but they technically could not offer precise images of the structures of the nose and sinuses at all. The problem is worse since even nowadays, after decades of the use of CT scanning techniques, the radiologists generally never mention this anatomical detail in their findings; they simply skip this since they haven't ever been, during their education, introduced to the concept of the existence of some space, empty or filled, within the nasal septal skeleton. The fact is that the diagnoses like "mucocoelae" or "mucopyocoelae" of the "sinus septi nasi" or "sinusitis sinus septi nasi" are extremely rare and sound a bit weird. This is why such diagnoses practically do not exist in everyday clinical practice as well as in the rhinologic literature.

The biggest enigma is from where exactly this formation within the perpendicular lamina develops. In cases of some spaces that give an impression that it goes for a kind of sinus within the perpendicular lamina, it could be presumed that it derives from the sphenoid sinus like the pneumatization of the crista galli was proved to do [2]. Whether or not there is any communication between sinus septi nasi (SSN) and the adjacent paranasal structures is not known yet. Clinical experience, however, says that from time to time the careful observer of the CT scans can perceive a kind of strange space within the bony skeleton of the nasal septum, almost always filled

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_2

with a grayish mass (Fig. 2.1). A case of mucopyocele within SSN has been successfully operated a few years ago. Owing to the CT scanning techniques of nowadays, there is no obstacle for this clinical entity to rapidly come into the focus of interest of modern rhinologists.

Mladina's study [3] on this subject showed two types of findings:

(a) Pneumatized tumefaction, i.e., an empty space within the bone of the ethmoidal plate surrounded by well-visible and clearly defined bony walls. This finding has been named "sinus septi nasi" (SSN).
(b) Non-pneumatized tumefaction located at the same position as the SSN, filled with a spongy bone only. It was simply named "spongy bone" (SB).

The results of this study showed SSN in 32 out of 93 skulls (34.40%). Among them, there were 23 male (71.87%) and 9 female skulls (28.12%). The width of the SSN formations varied from 0.5 to 4.2 mm, and the length varied from 3.5 to 18.8 mm, whereas the height varied from 3.8 to 17.7 mm.

Tumefactions filled with the spongy bone (SB) have been found in 61 out of 93 skulls (65.59%). They were not suitable for precise measuring since the outer borders were not strictly and well defined at CT scans, perhaps as a consequence of the process of preparation of the cadaveric skulls.

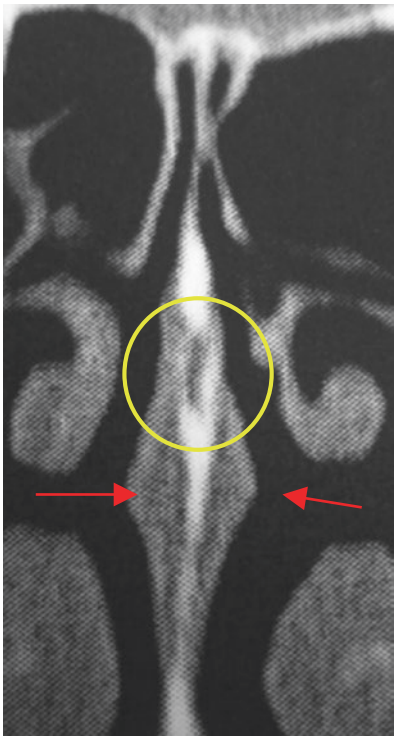

Fig. 2.1 A coronal CT scan of the paranasal sinuses. There is an obvious grayish, vertical, and oblong area within the bone of the perpendicular lamina (within the yellow circle), whereas the swelling of the septal mucosa underneath this anatomical detail is quite emphasized (red arrows). This has been named in clinical practice as "tumor septi nasi" for decades during the pre-CT era. It looks like the anterior rhinoscopic finding in Fig. 2.2

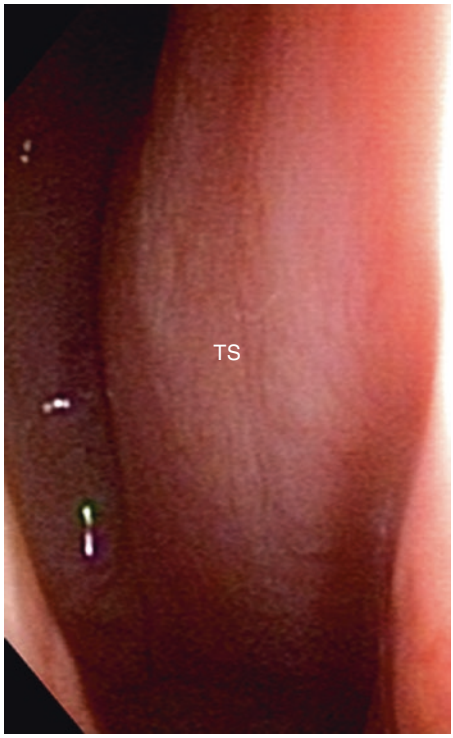

Fig. 2.2 Left nasal cavity. TS: belly-like tumefaction of the upper parts of the middle areas of the nasal septum can be found in patients with the sinus septi nasi

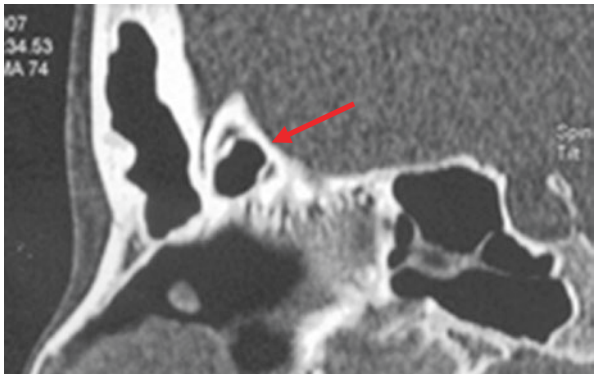

Fig. 2.3 A pneumatized crista galli (red arrow)

On the other hand, we also have the question of the possible pneumatization of the crista galli, suggesting another possible sinus that is not so frequently mentioned in the literature. Crista galli is an anatomical structure localized in the midline above the cribriform plate, having a posterior border, thin and slightly curved, with the falx cerebri attached to it, and a much thicker and shorter anterior border, attaching to the frontal bone by two small alae, taking part of the formation of foramen caecum [4] (Figs. 2.3 and 2.4).

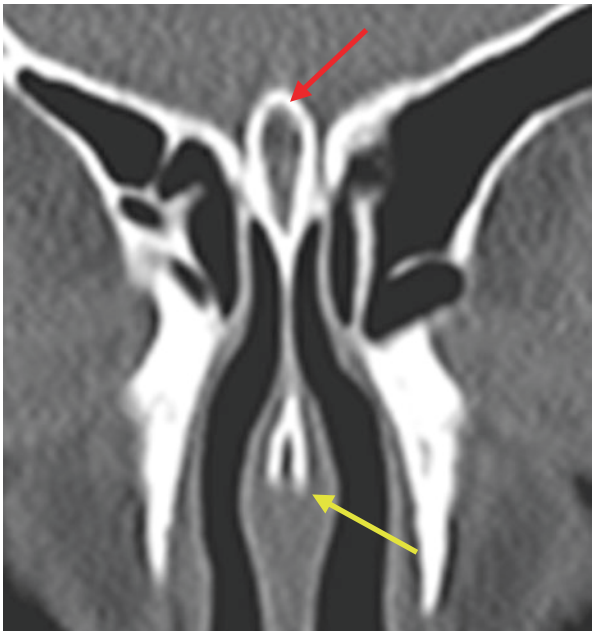

Fig. 2.4 A coronal CT scan of the paranasal sinuses showing noticeable pneumatized crista galli (red arrow). The radiological signs of the existence of sinus septi nasi (in this very scan presented as a downward directed fork-like bony formation) (yellow arrow) are also perceivable

Crista galli in some subjects is a homogeneous bone, but like the perpendicular plate of the ethmoid bone in the nasal septal skeleton, it can also be pneumatized. The incidence of a pneumatized crista galli varies from 3% to 37.5% [5–10]. Time and again, all reports have been based on studying both coronal and axial CT scans of the paranasal sinuses. The pneumatization of the crista galli could originate either from the ethmoidal sinus or from the frontal sinus itself [5]. The communication between pneumatized crista galli and the adjacent paranasal structures usually happens through an opening similar to other sinus ostia, usually to the frontal sinus cavity. In case of ostial blockage, an inflammatory response, similar to rhinosinusitis, can occur. Socher et al. [6] reported three clinical cases in which chronic, stubborn frontal headache was found to be generated from the inflamed sinus within the crista galli. Socher and his team endoscopically removed the diseased, swollen mucosa, found within the sinus crista galli, in all three cases, and the outcomes have been excellent. So, according to these results, the answer to the question from the title of this chapter which says "do additional sinuses matter?" is "yes, they absolutely do!"

2.2 Conclusion

In conclusion, we can say that two additional sinuses can exist in man and can play a clinical role, particularly as the sources for so-called focalosis. Regardless of that, in cases of diseased sinus septi nasi, the most frequent complaints that can be heard from the patient are headache, mostly located in the frontal region and the region of

the root of the nasal pyramid, prickling in the eyes (while the ophthalmologic findings are in rule normal!), and in cases of emphasized, belly-like septum, the patient also can experience difficulties in nasal breathing. In cases of diseased sinus cristae galli, the most frequent symptoms are again headache, mostly located in the parietal region, sometimes of pulsating character. In some patients, disturbances of olfactory function can appear, as well as a sense of the pressure on the eyeballs.

Time and again, yes, so-called additional (but, in fact, neglected, underestimated, and, for very many colleagues, unfortunately, unknown) sinuses do matter!

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What Is Nasal Hyperreactivity?

3

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3.1 Introduction

One definition of nasal hyperreactivity (NHR) is: "the induction of one or more nasal symptoms like rhinorrhea, sneezing/itch, or obstruction upon encounter of environmental stimuli, such as cigarette smoke, temperature/humidity changes, strong odours/fragrances, and other irritants" [1, 2]. NHR may feature in every kind of rhinitis, irrespective of aetiology, including coryza (due to an infection), nonallergenic rhinitis (NAR) or allergic rhinitis (AR) [3]. Segboer et al. [3] examined two groups of patients for NHR: those with NAR (408 individuals) and those with AR (585 individuals). The reported frequency was 66.9% in the first group and 63.4% in the second.

Currently, it appears that chemical (irritant) causes for NHR (smoking, perfumes, cleaning materials) produce the same generalised disturbance of the mucosa lining the nose and upper airways as physical causes, such as changing temperature, exercising, being under stress or in humid conditions [3]. The situation thus appears to resemble that found in conditions producing hyperresponsiveness of the bronchi, such as asthma or COPD (chronic obstructive pulmonary disease), where both chemical and physical triggers produce identical mucosal alterations [4]. Indeed, most cases of untreated airway disease, affecting all portions of the tract (rhinitis and asthma), are said to feature mucosae that are hyperresponsive [2, 5].

NHR involves the mucosal surface of the nose showing heightened reactivity towards nonspecific triggers of a chemical or physical kind, including abrupt

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_3

alterations in temperature, smoking fumes and chemical agents [1, 6]. NHR is seen in conjunction with nasal inflammation, which may arise from colds, AR or NAR of persistent type [7–9].

The type or quantity of stimulation did not vary between cases of AR and NAR. Being sensitive to a physical trigger did not preclude a similar response to chemical irritants. The reverse was also true. Patients with both AR and NAR were sensitive to cold, dry air provocation (CDA), the test resulting in worsened symptoms and rhinorrhoea, but the same test did not provoke a reaction in healthy controls.

3.2 The Pathophysiology of NHR

It is hypothesised that NHR comes about through changes in the pattern of nervous input to the nose [10]. The nervous supply and functioning of the upper air passages is complicated, with multiple pathways acting upon each other. The baseline state of the upper airways is regulated through the autonomic (sympathetic and parasympathetic) nervous system. This is the same system which oversees control of the epithelia, blood vessels and glands [11].

The sympathetic innervation mainly supplies blood vessels, with some secretomotor supply also found. The nerve terminals release noradrenaline and neuropeptide Y (NPY), resulting in decreased blood flow and reduced secretions from the nose [12]. The parasympathetic innervation targets both the vasculature and the exocrine glands of serous and seromucous type found in the mucosa of the nose. The nerve supply to these glands is profuse. Nerve terminals secrete acetylcholine and neuropeptide substances, including vasoactive intestinal peptide (VIP). The combined effect of these neurotransmitters is to heighten blood flow and increase secretory activity in the nose, which gives rise to a congested nose. VIP targets two receptors: VPAC1 (type 1) and VPAC2 (type 2). Binding of VIP causes secretory activity by the glands to increase [11].

3.2.1 Potential Mechanisms Whereby NHR Occurs

3.2.1.1 Epithelia Become More Permeable

One theory holds that injury to the epithelial surface renders the barrier less effective and therefore brings a greater amount of stimulus into direct contact with sensory nerve terminals, the vasculature and the glands lining the nose. Although Buckle and Cohen [13] recorded that ^{125}I-albumin was able to pass the mucosa of the nose more readily in subjects suffering from rhinitis than in healthy volunteers, this finding has not been replicated in more recent research. Plasma seeps into the tissue as part of the inflammatory reaction when allergens are present either artificially [14] or naturally [15]. However, despite plasma proteins being present in the extravascular compartment, a labelled substance, ^{51}Cr-EDTA, showed no signs of being absorbed more readily than is the usual

case. On the contrary, seasonal AR [16] or coryza [17] may actually result in the mucosa being less permeable than usual.

3.2.1.2 Changes in Neuromodulation

Upgraded neural sensitivity is one mechanism by which innocuous stimuli can trigger hyperreactivity. Specific signalling molecules increase the sensitivity of nervous transducers. Examples include the prostaglandins and the peptidoleukotrienes [18]. Stimulating the autonomic system via isotonic or isometric exercise, exposing the facial region to low temperatures or pressing on the axilla creates a different response in individuals with NAR than in healthy individuals [19].

Some researchers suggest that NAR arises from improper balancing of the sympathetic and parasympathetic systems and that NHR in the absence of allergic hypersensitivity is down to autonomic dysfunction [1].

3.2.1.3 End-Organ Hyperresponsivity

It is possible that hyperresponsivity in glandular tissues or blood vessels may be due to changes in sensitivity. Research has demonstrated that the response to methacholine is enhanced in allergy sufferers, thereby increasing secretion [20]. NAR cases also sometimes have a response to methacholine [21] but only where rhinorrhoea is the principal presenting problem. Since methacholine acts directly on the glands within the nose and does not depend for its action on nervous systemic action, such a result is evidence that muscarinic receptors are either more numerous or bind more avidly in hyperresponsive individuals [22].

The neurotransmitters VIP and NP-Y modulate the tone in blood vessels, but neither molecule activates either cholinergic or adrenergic receptors. Adrenergic action normally leads to vascular constriction [19]. AR was not associated with alterations in adrenergic receptors of alpha or beta type [22]. Nerves that can be stained to show receptors for VIP are present in greater abundance in cases of AR than in either NAR sufferers or healthy individuals [23].

Svensson has demonstrated that microvascular exudative hyperresponsiveness is a feature of seasonal AR when birch pollen aeroallergens are present [24]. The effect of administering histamine at concentrations of 40 and 400 μg/mL during the pollen season, or at other times, was studied. Serum concentrations of alpha-2-macroglobulin and albumin rose at the level of statistical significance in the season compared to other times. Nasal lavage was used to obtain the fluid for sampling. A number of factors have been proposed to account for the capillary response, including sensitisation of endothelium lining venules, disappearance of normal restraining influences on endothelium and disruption of nitric oxide signalling [1].

3.3 Diagnostic Tests

Despite being present in between approximately 60–70% of cases of rhinitis, irrespective of subtype, NHR is rarely attended to clinically since no useful test for the condition exists. In the past, tests that relied on provoking a response in the nose

were written about, but no suitable test actually entered routine practice [25–31]. The principal explanation for this failure is the lack of a suitable format convenient for both clinicians and patients and low sensitivity and specificity of the tests developed [2].

There are reports indicating the use of a variety of experimental methods to provoke a nasal reaction and diagnose NHR, including hyperosmolar solutions [25, 26], histamine [28, 32] and capsaicin [30, 33]. Nasal lavage has two key disadvantages as a way to demonstrate NHR, which make it unsuitable in practice: first, it produces mechanical disturbance of the mucosa and thus may artificially provoke symptoms; second, it is only possible if the patient is very willing to allow it to be done, which rarely happens [2].

The use of cold, dry air (CDA) was the method which caused the least discomfort to the patient, was the safest and disturbed the normal physiology to the lowest extent [27–29, 31]. This method has the further advantage that it involves inhalation, rather than instillation, into the nasal cavity.

Braat et al. [28] proved the benefit of using CDA rather than histamine to stimulate a nasal reaction in discriminating a group of cases of IR from healthy controls. Whilst using CDA had a lower sensitivity than histamine application (87% vs 100%), its specificity was 71%, whilst that of histamine was zero [24]. CDA had the further desirable feature of being highly reproducible in terms of altering nasal patency and bringing about excess nasal secretions [28]. Despite all this, the method takes so long to perform (over three quarters of an hour) that it is unlikely to suit most clinical settings [2].

3.3.1 Nonspecific Nasal Provocation Testing with Direct Stimuli

3.3.1.1 Histamine

Histamine exerts its effects by direct action on the receptors embedded in the epithelial surface, thereby triggering the trigeminal reflexes modulating blood vessel tone and gland secretions. It possesses the highest potency amongst signalling molecules. Congestion and oedema result from histamine-induced vasodilation, and nasal secretions increase. Histamine invariably induces hypertension, flushing, an increase in heart rate and headaches. Whilst atopic persons tend to react more severely to histamine than healthy controls and a dose-response relationship is evident in the mucosal response to histamine, there is no clear separation in the parameters measured for each group and thus no way to distinguish on this basis between those with rhinitis and those who are normal [34].

3.3.1.2 Methacholine

Methacholine is an artificially created molecule that acts in a similar way to acetylcholine. Its principle action is to stimulate cholinergic receptors on the gland. In this way, it causes excessive nasal secretion and blockage to occur [34].

Borum investigated the effects of supplying methacholine at concentrations between 3 and 48 mg/mL through a nebuliser to individuals with chronic rhinitis

[35]. Posterior rhinomanometry indicated that the resistance to airflow through the nose did not alter. However, the level of secretion did vary, and the authors used this finding to argue that this parameter held greater clinical value and was more reliable than resistance to airflow. If anticholinergics were given before methacholine, the response was muted, whereas lidocaine did not alter the response.

Naclerio and Baroody [36] contrasted methacholine challenge with histamine challenge in a cohort of chronic rhinitis sufferers. Discs of filter paper were impregnated with different amounts of either methacholine or histamine, and the resulting level of secretions from the nose was recorded. For both substances, a dose-response curve was obtained. Nonetheless, histamine produced effects that methacholine did not, i.e. tachyphylaxis and a secretory response on the other side of the nose, that may be due to a parasympathetic reflex action and would be abolished by the administration of anticholinergic agents, e.g. atropine or ipratropium bromide.

3.3.2 Nonspecific Nasal Provocation Testing Via Indirect Stimulation

3.3.2.1 Adenosine 5′-Monophosphate

The enzymatic action of 5′-nucleotidase on endogenous intracellular adenosine 5′-monophosphate (AMP) results in the production of the nucleotide, adenosine. Adenosine is raised in inflammation. AMP is known to be important in the way asthma and AR develop and is present at a raised level in asthma cases. Whilst the inhalation of adenosine in healthy volunteers produces no constriction of the bronchi, in cases of asthma, it does lead to constriction, as has been shown in earlier research [37].

Signalling molecules of importance in the inflammatory response, e.g. histamine, cysteine, prostaglandins, leukotrienes and interleukins (IL-8), are released from mast cells when their A2b receptors are activated by AMP. If inflammation is of the allergic type, the AMP-dependent response is heightened, potentially due to higher levels of activated mast cells [34].

Rhinitis cases have more severe symptoms and higher levels of mucosal histamine when stimulated with AMP than healthy volunteers [34]. Even after a single administration of AMP at a dosage of 6.5 mg, this result was evident, according to Polosa et al. [38]. Histamine was elevated significantly when measured in nasal washings from atopic individuals taken 3 min after administration of a single spray in each nostril of an AMP solution at a concentration of 50 mg/mL. This effect was not observed in healthy volunteers.

Using AMP to investigate NHR seems to have greater sensitivity than administration of either histamine or methacholine. AMP administered nasally is a method with acceptable safety, sensitivity and reproducibility, albeit the method lacks a standard format, with different researchers reporting varying concentrations and ways to administer the AMP [34].

3.3.2.2 Cold Air

Cold-air rhinitis is where being exposed to low-temperature air causes a runny nose, nasal blockage and burning sensations. Individuals thus affected may already have rhinitis or not. Cold air alone may trigger symptoms. Normal nasal physiology means that air passing through the nose is both heated and humidified, a process carried out by the mucosa, which, as a result, tends to dry out and undergo cooling [34]. Vasoconstriction makes the mucosal temperature fall, whilst topical anticholinergic agents (e.g. ipratropium bromide) make the mucosa function better to heat and humidify inhaled air. They also diminish secretions when air at low temperature is inhaled through the nose [39].

If the autonomic pathways are stimulated, such as by administering cholinergic agents, or if inflammation is present, there will be greater levels of secreted water and chloride ions in the airway [34]. Assanasen et al. [40] noted that, following encounter with allergens, the epithelium had an enhanced capability of delivering water. If corticosteroid therapy had been given 2 weeks previously, there was no such enhanced water excretion.

Testing for NHR with cold inhaled air is straightforward but is neither sensitive nor specific, although earlier it was accepted that it had a high specificity and sensitivity. It may be of benefit for understanding the physiology of the nose and show the way to investigate these phenomena as they occur within the bronchi [34].

3.3.2.3 Mannitol

Mannitol can act as a hyperosmolar stimulant, resulting in signalling molecule release. It is not fully understood how the pathophysiology works, but mast cells, the mucosal epithelium and C fibres of the CNS are hypothesised to be implicated [41]. Koskela et al. [41] took three groups of people—AR cases with symptoms, AR cases without symptoms and healthy volunteers—and administered mannitol solution (200 mg/mL) to the nose. Whilst a burning feeling was felt by all the participants, only the AR cases went on to develop nasal congestion and raised 15-HETE (15-hydroxyeicosatetraenoic) acid levels. This research found that nasal stimulation with mannitol principally exerts its effects through epithelial cells.

3.4 Treatment of NHR

Despite being a feature of multiple disorders affecting the nose, there is no standardised way to treat NHR, according to the literature. The ARIA guidelines [42] are used clinically to guide treatment of NHR in cases of AR, whilst corticosteroid therapy to the nose is frequently given for NHR in NAR or IR. This has varying levels of success [42–46].

Van Rijswijk et al. [47] found that capsaicin (an irritant substance found in chilli peppers) applied to the nasal cavity reduced NHR in cases of IR. Capsaicin is a TRPV1 agonist. These findings have been replicated in another study [48], which also discovered other clues about the way this treatment achieves its benefit. The latest Cochrane Review on the subject [46] suggests that, in the absence of truly

effective therapies for IR, a trial of capsaicin under medical guidance is reasonable. Up to now, trials of capsaicin have not proven their benefit in AR. One explanation for this is that the pathophysiology of AR mainly hinges on IgE. In addition, TRPV1 levels in AR are not raised [49].

An investigational drug, SB-705498 (in the form of 3% topical cream for the nose), was trialled on healthy human volunteers with itching provoked by histamine or velvet bean [50]. The outcome was negative. The negative outcome is unsurprising given that the activity of TRPV1 and neuropeptide substance P is normal in healthy people. In contrast, capsaicin treatments in the nose at a concentration of 0.1 mmol/L have effects not simply on TRPV1 but also on a range of TRP-channel-linked pathways (e.g. TRPA1) found on afferent fibres [2].

It has now been shown that azelastine has effects on how TRPV1 works by modifying calcium-linked signal function in neurones of sensory type and the epithelial cells of the nose [51]. Since cholinergic receptors of muscarinic type are found in association with TRPV1 [52], it has been argued that agents with anti-muscarinic activity, such as tiotropium, may have a part to play in NAR.

A recent study has shown that the combination of azelastine with fluticasone propionate in the form of Dymista successfully treated NHR [53].

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What Is Vasomotor Rhinitis?

4

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4.1 Introduction

The use of the term "vasomotor rhinitis" has been abandoned in many countries and guidelines because it assumes a mechanism of vascular changes which do not exist. The condition previously described by the term VMR is a form of neurogenic nonallergic rhinitis. Nonallergic rhinitis (NAR) encompasses rhinitis symptoms without allergic sensitisation or infectious aetiology. Two major subtypes exist: an eosinophilic inflammatory endotype including nonallergic rhinitis with eosinophilia (NARES), local allergic rhinitis (LAR) and NSAID-exacerbated respiratory disease (N-ERD) and a neurogenic endotype which includes gustatory rhinitis, rhinitis of the elderly and idiopathic rhinitis. This second endotype includes what was called VMR.

Vasomotor rhinitis therefore can be defined as a nonallergic type of rhinitis not connected to allergic responses, infective agents, anatomical anomaly, systemic disorders or drug misuse [1]. The diagnosis is made after excluding other potential diagnoses and after negative allergy testing. There may be multiple causes. In this chapter, VMR will be defined as an essential, chronic, nonallergic pattern of rhinitis in which cutaneous allergy testing is negative, there is no rise in serum IgE and nasal cytology fails to show evidence of inflammation [1, 2].

Nonallergic rhinitis (NAR) is presently diagnosed only following the exclusion of other disorders. Before it can be confidently claimed that a patient is suffering from

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_4

vasomotor rhinitis (VMR) or nonallergic rhinitis with eosinophilia syndrome (NARES), the full range of nonallergic rhinitis disorders needs consideration and exclusion [1, 2]. Specific IgE should not be demonstrable in skin prick testing, serologically or through allergen challenge testing for entopic (local allergic) responses, if NAR is the putative diagnosis. Typically, irritant substances such as smoking fumes or perfumed cosmetics and variation in temperature and atmospheric pressure will worsen NAR symptomatology [1]. Whether eosinophilic infiltration of nasal mucosae has occurred or not is the key differentiator between VMR and NARES, the latter being an inflammatory disorder not linked to allergy, whilst the former is neither inflammatory nor allergic in aetiology [2]. History and examination alone cannot distinguish between AR and NAR, as both conditions may be identical in their presentation [3, 4].

NAR is a frequently encountered disorder in which there is persistence of at least one of the following symptoms: congestion of the nose, nasal discharge or postnasal drip. The diagnosis depends on excluding other potential causes of these symptoms, e.g. allergic disorders, infection, side effects of medication, anatomical abnormality, endocrine disorders, vasculitis, metabolic problems or nasal atrophy [5].

The clinical features of NAR which set it apart from AR include [5]:

- NAR starts later in life.
- There is no nasal or ocular pruritus. Sneezing is not marked.
- Nasal stuffiness and postnasal drip are conspicuous.
- The symptoms of NAR occur year-round.

Irritating substances (powerful fragrances, smoking, cosmetics, diesel or automotive fumes) are the usual precipitating factors in NAR, and sufferers may describe nasal stuffiness experienced in heavy traffic. Other triggers are cleaning substances, newspaper ink, temperature change and ethanol-containing drinks [4]. There are several subtypes of NAR:

- VMR (vasomotor rhinitis). In VMR, symptoms are sporadic and consist mainly of congested nasal passages and rhinorrhoea. Irritant substances (airborne pollutants) provoke a vigorous response, as do alterations in surrounding temperature, particularly if the air inhaled is dry and low in temperature [6].
- Gustatory rhinitis. Here pungent foodstuffs cause a sporadic watery nasal discharge through activation of cranial nerve X [7].

4.2 Classifying NAR

The following scheme is used to classify NAR [8–10]:

- Syndromes where the aetiology has not been established
  - Vasomotor rhinitis
  - Nonallergic rhinitis with eosinophils (NARES, BENARS)
  - Basophilic/metachromatic nasal disease

- Syndromes where the likely cause has been discovered
  - Chronic sinusitis
  - Deficiency syndromes of the immune system
  - Blockage of the ostiomeatus
  - Metabolic conditions
  - Oestrogen as a factor (birth control pills, hormone replacement therapy, being pregnant)
  - Underactive thyroid
  - Acromegaly
  - Vasculitides/autoimmune and granulomatous diseases
  - Sjögren's syndrome
  - Systemic lupus erythematosus
  - Relapsing polychondritis
  - Eosinophilic granulomatosis with polyangiitis
  - Sarcoidosis
  - Granulomatosis with polyangiitis
- Medication-related
  - Topical decongestants
  - Drugs with a systemic action
- Rhinitis associated with polyp formation in the nose
  - Aspirin intolerance
  - Chronic sinusitis
  - Eosinophilic granulomatosis with polyangiitis
  - Young's syndrome (disease of the sinuses and lungs, azoospermia, polyp formation in the nose)
  - Cystic fibrosis
  - Kartagener's syndrome (abnormal bronchial widening, persistent sinusitis, polyp formation in the nose)
- Rhinitis linked to anatomical abnormality
  - Deviated septum
  - Distorted turbinate architecture
  - Malfunctioning nasal valve
  - Hyperplastic adenoid growth leading to blockage
  - Injury-related (e.g. leakage of cerebrospinal fluid via the nose)
  - Congenital
  - Cancer-related
- Atrophic rhinitis
  - Postsurgical
  - Atrophic rhinitis per se
- Related to irritant triggers of chemical or physical type
  - Desiccated air
- Gustatory
- Intense light
- Polluted air
  - Occupational

- Occupational rhinitis
  - Subjective feeling
  - Irritant
  - Immune-related
  - Exposure to corrosive agents

4.3 Pathophysiology of VMR

The precise pathophysiology of VMR has so far remained mysterious. The most that can be said is that the nose exhibits a non-specific hyperresponsiveness to triggers of a non-immunological type, such as alteration in temperature or air moisture content, consumption of alcoholic beverages, powerful odours and aerosolised irritants. The mucosal lining of the nose appears in laboratory settings to be hyperresponsive to methacholine [11], capsaicin [12] and histamine [13], but why this should be so is unknown. Chronic nonallergic cases of rhinitis have elevated levels of mastocytes, but new research has revealed that goblet cell levels are normal. There is no difference in mastocyte numbers between individuals with or without allergy [14, 15].

The pathology of persistent VMR is not attributable to a single known cause. It is recognised that symptoms may begin with sufferers becoming more sensitive to environmental triggers such as temperature change, polluted air, powerful smells or fragrances. Nonetheless, new research has highlighted other factors that may underpin the pathophysiology. Amongst such factors are unappreciated local IgE production, inappropriately functioning pain receptors and autonomic malfunction [16].

4.3.1 Entopy: Local IgE Synthesis

Entopy is a state where allergy exists confined to a particular body locale, but systemic signs (skin prick testing, raised circulating total or specific IgE) are absent [17]. The fact that cells involved in the allergic response may be found in nasal mucosal biopsies lends credence to this theory. Whilst initial research on nasal biopsies which compared essential, nonallergic rhinitis cases with healthy controls failed to confirm differences in the levels of lymphocytes, antigen-presenting cells, eosinophils or any other cell-bearing IgE [18, 19], the use of intranasal steroid therapy may have confounded the results. Indeed, newer research which compared biopsy specimens from chronic NAR cases with healthy controls showed that levels of three different T-lymphocyte types were raised in the NAR cases: CD3+, CD25+ and CD45RA+ (=T-cells lacking exposure to allergens) [17].

IgE may be produced locally in NAR, and high-affinity receptors for IGE have also been found to be raised in some individuals with NAR [20]. Local IgE was found to be produced in tissue taken from cases of NAR and preserved in a nutrient medium [21, 22]. This would lead to reclassification of such patients as local AR, rather than NAR. Khan [23], however, has cast the notion of atopy into doubt. He

discovered that whilst 5 out of 20 chronic NAR cases were positive on first testing, repeated testing was uniformly negative [23].

4.3.2 Pain-Receptor Malfunction

The nasal mucosa is able to sense several types of stimuli (mechanical or chemical) and convey the perception through sensory afferent fibres to the cortex. Heat, cold and burning sensations travel by the fast Aδ fibres, whilst C fibres convey sensations of slight pain, paraesthesia and light touch [24]. C fibres may additionally transport sensation of stretch, if the epithelial cells become swollen or the nasal mucosal vascular supply becomes congested [25]. Particular molecules have specific receptors located on epithelium and on nerve terminals, activation of which can cause the neurones to fire. Signal molecules (bradykinin, histamine and amines) stimulate particular receptors. One receptor of interest is the TRPV1 (TRP vanilloid 1) (capsaicin) receptor. Not just capsaicin but alcohol, local anaesthetic agents and temperatures exceeding 42 °C may activate the receptor. Applying capsaicin to the nasal mucosa reduces nasal stuffiness in VMR more than in AR, implying a role for pain receptors in the pathophysiology of NAR [26].

The fact that cold, unmoist air produces nasal obstruction proportionally to the volume of gas inhaled in cases of essential NAR, a response not seen in either AR cases or healthy controls, is highly revealing [27]. The response mechanism occurs through an excessive degree of response by mucosally located nerve fibres conveying the sensation of cold in cases of essential rhinitis. This mechanism is utilised in the standard diagnostic test for essential NAR, which utilises acoustic rhinometry to see the effect on airflow resistance of inhaling unmoist, cold air [28]. The condition termed "skier's rhinitis" is characterised by nasal obstruction and prolific rhinorrhoea brought on by inhaling cold air. The condition is mediated through upregulated parasympathetic afferent circuits that use acetylcholine as neurotransmitter. The use of topical anticholinergic agents inhibits the reflex [29].

4.3.3 Autonomic Dysfunction

Some VMR may involve dysfunction of the autonomic system. One study looked at autonomic function in 19 cases of VMR and compared these cases with 75 matched controls [30]. The VMR cases scored abnormally on the subscores for sudomotor, cardiovagal and adrenergic activity. The researchers hypothesised that the best explanations for these scores were either decreased sympathetic action or unbalanced autonomic function. They believed this more credible than explaining the results on the basis of parasympathetic overactivity. One possible way such dysfunction might be induced is via injury to the nose [31]. Midfacial pain syndrome has multiple similarities with tension headache. In both cases, the pain follows a symmetrical distribution and may affect the nasal radix, the nasal bridge, around or behind the orbit and the cheeks. The history is of pressure affecting the nose, a

heavy or constricting sensation and sensing obstruction of the nares despite their remaining patent. Usually, neither CT imaging nor nasal endoscopy finds any abnormality [32].

4.4 Symptoms

VMR symptomatology usually involves nasal blockage or stuffiness and discharge from the nose. It is less usual to see sternutation or nasal itching. Research that examined 678 cases with rhinitis found that VMR was especially associated with nasal obstruction, but AR tended to be associated with sternutation, nasal discharge and itching affecting the eye. The AR cases were more likely to suffer from comorbid asthma [33]. Togias [34] found that cases of NAR tended to sneeze less and have fewer eye symptoms, but distinguishing between NAR and chronic AR was impossible on the basis of frequency of nasal discharge or stuffiness.

These symptoms might be year-round, chronic, periodic or confined to a particular time and may be triggered by changes in the weather, such as temperature changes and alterations in humidity or atmospheric pressure [35, 36]. It is worth observing that no clear trigger may be found for VMR, even if it is common to single out some precipitant, such as a fragrance or powerful smells [37].

Cases of VMR may be of two different types: a liquid discharge may predominate ("runners"), or obstruction may be the key feature ("blockers") [38]. The runners typically have symptoms mediated through cholinergic hyperresponsiveness. The blockers have pain receptors that respond in an exaggerated manner to an otherwise harmless stimulus [9]. As described above, the pattern of symptomatic response differs somewhat between NAR and AR patients [33], although with the limitations previously noted [34].

VMR usually occurs year-round, and the presence or absence of an allergen has no effect on the condition [39]. However, there may be some worsening of symptoms at particular times of year (i.e. spring and autumn), but these exacerbations are triggered by meteorological factors, not seasonal allergens, except in subjects with concomitant AR [4, 40]. VMR cases have sensitivity to a variety of factors that produce no response in healthy individuals. These factors include powerful smells, breathing in cold air, alterations in ambient temperature, changes in humidity or atmospheric pressure and consumption of ethanol [8].

4.5 Diagnosis

Diagnosis depends on obtaining an appropriate patient account and being able to exclude other types of rhinitis (AR, infective, inflammatory or immune-mediated). If a patient has the pattern of symptoms described in Sect. 4.4 and the rhinitis was triggered by the usual precipitants, it is probable they have VMR [41].

Typical mucosal appearances do not differ from the normal, although some cases have a red-appearing or beefy mucosa [42]. Nasal eosinophilia or circulating

eosinophilia should not be present, nor should prick testing be positive. Circulating specific IgE titres should not be raised. Total circulating IgE will typically not be raised, either [8].

Not having a previous history of an atopic disorder either in the patient or their family members is supportive of VMR as the diagnosis. In individuals above the age of 35 who have no previous atopic history, where there is no seasonal pattern identifiable and no allergen seems responsible and where the precipitant is non-specific (e.g. fragrances set it off), there is above 99% chance that they have VMR [4].

4.6 Treatment

In cases of known VMR, avoidance of the factors that set off symptoms is key. For example, certain smells (smoking fumes, fragrances, bleach or formaldehyde), traffic exhaust, strong light, changes in ambient temperature and pungent or spicy foodstuffs may be the triggers to avoid. Persistent VMR cases benefit less than those with AR from medication [43–45]. Intranasal corticosteroids and locally applied azelastine (an antihistamine) are useful in general for symptomatic management of the conditions grouped under the NAR label. Ipratropium bromide has an indication for treating nasal discharge [8].

In cases with nasal discharge and stuffiness, topical histamine blockers (azelastine, for instance) are beneficial. It is also possible to combine this with a locally applied intranasal corticosteroid, should monotherapy with either agent prove insufficient.

Two possible treatment approaches to VMR are to aim for a general improvement across all symptoms ("broad-based" treatment) or to aim to manage a particular symptom. Given that VMR may present with a broad range of complaints, from those affecting nasal patency to those producing discharge, a broad-based approach may offer greater benefit. Agents suitable for the broad-based approach include locally applied corticosteroids or azelastine [8].

4.6.1 Intranasal Glucocorticoids

Therapeutic use of intranasal steroids is effective on inflammation of whatever cause. Clinical efficacy in AR, certain types of NAR (including VMR) and chronic rhinosinusitis has been adequately proven. A study involving 983 cases of NARES and non-NARES examined the effect of fluticasone propionate at doses of 200 and 400 μg vs the effect of placebo. Both doses showed superiority to placebo, with no significant difference in efficacy between doses [46]. Fluticasone propionate remains the sole intranasal corticosteroid agent licensed by the US FDA for the management of both AR and NAR [47].

Agents that are FDA-approved for use in NAR include the budesonide inhaler, beclometasone nasal spray and fluticasone nasal spray. Locally delivered intranasal steroid therapy has a global effect on the symptoms of rhinitis and does not target a

particular symptom. One theory holds that intranasal corticosteroids will have greater efficacy in cases where mucosal inflammation is a component of rhinitis, since steroids have an anti-inflammatory effect. In a study investigating pharmacological actions of fluticasone spray in NAR, beneficial effects on inflammatory cells present in the nose and on cytokine release were demonstrated when the agent was administered to one side of the nose. The effect was present in cases of AR and NAR [48]. Specifically, fluticasone caused a statistically significant decrease in CD3+, major basic protein+ and tryptase+ cell numbers in individuals with AR or NAR compared to controls. There was downregulation of interleukin-4 and interleukin-5 mRNA on the side where fluticasone was applied. This result supports the notion that VMR may be treated with a trial of the use of intranasal steroids over a period lasting 2–4 weeks [49–51].

4.6.2 Antihistamines

From theoretical considerations, it may be anticipated that antihistamines with significant anticholinergic activity would have greater effect on nasal discharge than those with minor cholinergic action. Thus, first-generation antihistamines are expected to reduce rhinorrhoea more than second-generation (non-sedating) agents, and this is indeed the case: second-generation antihistamines have no demonstrable benefit in NAR. Histamine blockers given orally typically do not aid nasal congestion in AR, nor are they likely to assist in NAR. Whilst combining histamine blockade with decongesting agents could feasibly lessen VMR-associated congestion, this combination is off-label in the USA. However, on the basis of clinical experience, such a mixture may be thought beneficial in VMR [47].

Unlike their oral counterparts, intranasally administered antihistamines do possess considerable efficacy for the treatment of AR. Azelastine and olopatadine have FDA-licensed indications for seasonal AR. Azelastine has a licence for VMR. Although azelastine is classified as an antihistamine, the benefit in VMR and NAR is likely to be attributable to inhibition of the (neuro-)inflammatory response rather than to its antihistaminergic activity. In support of this conclusion, it has been proven that azelastine results in low levels of pro-inflammatory neuropeptide in the epithelium lining the nose. It also lowers the level of cytokines involved in inflammation, leukotrienes and molecules that promote cellular adhesion. Mast cells are also prevented from releasing their granules [52].

RCTs have confirmed the effectiveness of locally applied azelastine [53, 54], with two RCTs with placebo control conducted in multiple centres indicating symptomatic improvement in all areas within the initial 7 days for which treatment was given [54]. The inhibition of the inflammatory response seen with azelastine may be accomplished through reduction in eosinophilic recruitment, lower levels of adhesion molecules and reduced cytokine production [55, 56]. Initially, azelastine is given b.d., with two pumps per nostril.

Azelastine has an overall inhibitory effect on inflammation [55, 57–60]. Different studies have highlighted different aspects of the pharmacological action. Azelastine

diminishes the effectiveness of neurokinins (substance P and vasointestinal peptide) and stops discharge of histamine granules in vivo and in vitro [49]. Eosinophilic recruitment is lessened, and fewer adhesion molecules are manufactured [51]. The agent inhibits production of pro-inflammatory cytokines and NO by suppressing nuclear factor-B (NF-KB) [58]. Vascular permeability also decreases [57]. It appears, therefore, that azelastine can influence inflammatory messengers at the transcription level, alongside its originally known actions of preventing histamine degranulation, influencing calcium transportation and preventing migration of inflammatory cells in an allergic response. Quite possibly the benefit seen in VMR comes from a range of pharmacological actions, particularly the inhibition of cytokine synthesis [10].

4.6.3 Ipratropium Bromide

Ipratropium bromide (0.03%) nasal spray is suitable for cases of VMR with prolific nasal discharge. It is usual to advise two pumps in each nostril t.d.s. Usage can also be pro re nata or in anticipation of known triggers (such as cold air) or prior to eating. Ipratropium bromide is also available as double strength (0.06%), but the indication for this preparation is brief use for the management of, e.g. nasal discharge secondary to coryza [61, 62].

4.6.4 Decongestants

There is no published research examining how efficacious decongestant use is in persistent VMR. It is reasonable to attempt a trial of decongestant if the agents mentioned above fail to resolve the situation. Provided there is no past history of hypertension, pseudoephedrine may be tried for a brief period. Typical doses of pseudoephedrine in this situation would be 30–60 mg p.o. up to a maximum t.d.s.

4.6.5 Nasal Saline

Nasal lavage or the use of saline spray on a daily basis can be recommended just before using nasal steroids or azelastine. This recommendation also applies to post-nasal drip cases. Efficacy has been shown in both NAR and chronic rhinosinusitis [63–65]. Both sneezing and stuffiness may be relieved.

4.6.6 Intranasal Capsaicin

Capsaicin applied directly to the nasal mucosa is a therapy under experimental use [12]. Capsaicin is a powerful agent obtained from chilli peppers. Capsaicin is an agonist of the selective transient receptor potential vanilloid 1 (TRPV1) ion channel

and reduces nerve conduction of trigeminal nociceptive C fibres. It is unique since the initial neuronal excitation is succeeded by a refractory period during which TRPV1 expression is decreased. A Cochrane review [66] concluded that capsaicin is a reasonable option under supervision in idiopathic rhinitis, but there is no evidence that it helps in other forms of nonallergic rhinitis. Five applications in 1 day given under local anaesthetic cover reduce symptoms and nasal hyperresponsiveness for several months [67].

4.6.7 Topical Silver Nitrate

Applying silver nitrate at a strength of 15–20% may also be of benefit [68, 69].

4.6.8 Surgical Approach

Two possible operative approaches are available: sectioning the vidian nerve by means of the endoscope or electrocoagulating the anterior ethmoidal nerve [67, 70]. Both procedures aim to cut the parasympathetic innervation of the lining of the nose, with the aim of diminishing nasal secretory activity. Whilst symptoms may recur when the nerves regrow, the latest studies suggest the procedure is beneficial in the long term [71].

Blocking the sphenopalatine ganglion is also described in the literature as a palliative surgical procedure in VMR. The block needs to be performed between two and four times for complete resolution of symptoms [72].

Turbinectomy may also ameliorate congestion, although in the long term dryness and crusting are potential complications of the procedure, resulting from either enhanced airflow over the surface or the lack of protective secretions. If this progresses, atrophic rhinitis may eventually occur. Additionally, a subjective sensation of nasal stuffiness may still be present, even though the airway remains fully open in the nose [73]. Several operations are available to treat hypertrophy of the lower conchae; however, it is feared that the nasal lining may be unable to recover its full function following radical turbinectomy. Laser turbinectomy may not damage the mucosa in this way. Normal nasal cytology and saccharin transit times have been found following laser turbinectomy [5, 10].

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5 Cobweb Rhinitis: Arachnoidal Rhinitis—The New Clinical Entity in Rhinology

Ranko Mladina

5.1 General Considerations

The problem of diagnosing and treating vasomotor rhinitis can be complex, for two main reasons (Fig. 5.1):

1. The appearance of the nasal cavity during the anterior rhinoscopy and endoscopy of the nose is not necessarily always quite clear even to the experienced observer.
2. The reason(s) for the existence of swollen, dark-reddish-colored, or even pale nasal mucosa, be it bilaterally or unilaterally, cannot be always easily understood.

Fig. 5.1 Natural cobweb typically formed under the roofs of the country cottages

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_5

The goal of modern rhinology should require understanding of the etiology of some pathological finding. Therapeutics, particularly surgical skills, which can be used to "erase" the pathological finding without a true understanding of the reason of its appearance is no longer sufficient. Treatment should be directed to the cause of the pathological findings, not to them per se. Nowadays, the development of rhinology allowed us to understand that the nasal mucosa plays a role of the specific "mirror" of a number of pathophysiological events in the host, which thus requires a broader medical knowledge of young rhinologists as to enable the proper, clear diagnostic thinking in a broad field of possible reasons for the edema or, sometimes, even hypertrophy of the nasal mucosa. For instance, there is the real possibility to deal with the "hypothalamic vasomotor rhinopathy" in cases of suprasellar tumors of the pituitary gland or in those cases where the brain tumor is located in such a brain region that enables it to compress to the hypothalamus directly. This could disable emitting the action potentials from the vegetative nerve nuclei which, as far as we know, are located at the bottom of hypothalamus. In addition, other internal organs can also influence the volume and the function of the nasal mucosa. Among them are the suprarenal diseases (pheochromocytoma, for instance) and the gynecologic endocrinologic diseases (endometriosis, some hormonally active myomas, etc.). One should not forget that numerous cases of endometriosis of the nasal mucosa have been described not only in females but also in males. Furthermore, some of the disorders of the maxillary sinus drainage, like in two holes syndrome (THS), can influence the hypertrophy of the posterior half of the inferior turbinate owing to the permanent irritation by mucopurulent discharge coming constantly from the defect of the posterior fontanel toward the Eustachian tube orifice and nasopharynx, literally sliding over the mucosa of the posterior end of the inferior nasal turbinate (Figs. 5.2, 5.3, and 5.4).

The problem lies in the fact that still a vast majority of the rhinologists during the endoscopic examination of the nasal cavity just overlook the defect of the fontanel in the middle meatus, probably because they have been trained to consider it an

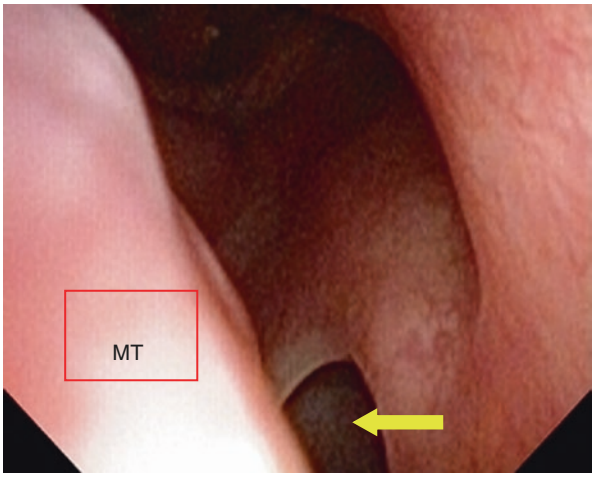

Fig. 5.2 The defect in the left fontanel (yellow arrow). *MT* middle turbinate

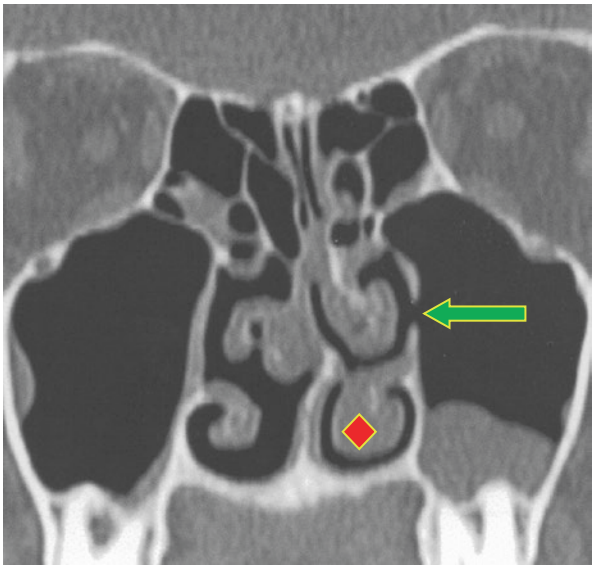

Fig. 5.3 The coronal CT scan showing the defect in the region of the posterior fontanel (two holes syndrome, THS) indicated by the green arrow, as well as a hypertrophy of the caudal half of the left inferior turbinate (indicated by the red sign)

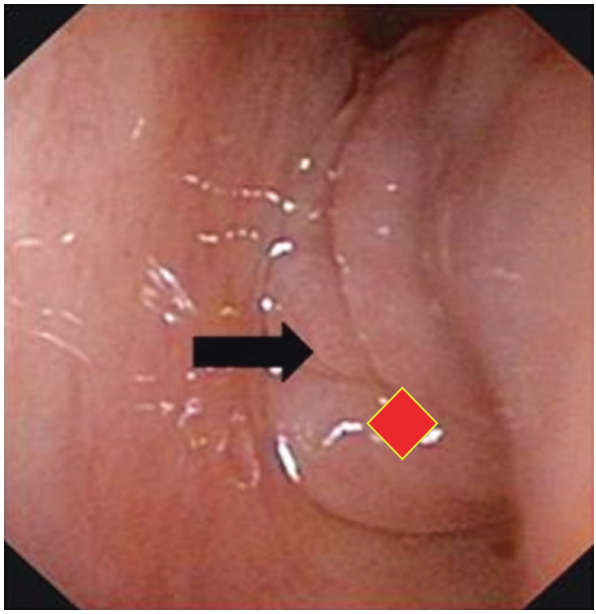

Fig. 5.4 The endoscopic view (0°) of the same hypertrophic caudal part of the left inferior turbinate shown in the CT in Fig. 5.3, hereby marked with the black arrow. The red sign indicates bully hypertrophy of the turbinate's mucosa that could be the consequence of the continuous irritation by the sliding down of sinus secretion coming from the defect of the posterior fontanel

"accessory ostium." This simply has been described in the literature for decades promoting the belief that the defect of the fontanel as an "accessory ostium" helps the drainage of the maxillary sinus itself. Unfortunately, they are not conscious of the fact that the defect of the fontanel is the same issue as the defect of the eardrum in chronic otitis media patients! This defect does not help maxillary sinus drainage,

and vice versa; it is the main prerequisite for the onset of the so-called recirculating mucus. Once healed from some acute purulent inflammation, the maxillary sinus continues its normal drainage (mucociliary transportation) toward the natural sinus ostium. The mucus comes out and begins to travel naturally toward the nasopharynx. But owing to the "trap," i.e., the defect of the fontanel, which is located at the mucus way toward the nasopharynx, it falls down into the sinus. The maxillary sinus mucociliary system works hard to eliminate it again from the sinus, but its mucociliary system is programmed to transport the mucus exclusively to the sinus ostium. It simply bypasses any other "hole"; it does not recognize it and goes directly to the natural ostium. This is why the suffix of the mucus comes out again and falls into the "trap" (so-called accessory ostium), and in this way a vicious circle develops resulting is the so-called recirculating mucus. In time, the amount of the recirculating mucus, which endoscopically looks like a mucosal ring (in fact, it endoscopically resembles a very lingeringly rotating merry-go-round), enlarges and slowly begins to partly detach from the main mass. After that, this piece of mucus mass goes down to the nasopharynx as a symptomatic postnasal drip!

It must be added here that radiologists almost never pay attention to the obvious discontinuity of the bony lateral nasal wall (Fig. 5.3), and neither have they almost ever described this morphologic finding in their reports!

Going back to the subject of this chapter, i.e., the cobweb rhinitis, it should be emphasized that during the last 10 years there are an increasing number of the patients complaining of subjective feeling of the bilateral nasal stuffiness where, at the same time, all of them have been showing an unusual clinical picture within the nasal cavities, resembling very much the spider web (a cobweb). There haven't been found any other possible mechanical obstructions like nasal polyps, septal deformities, or tumors. The cobweb in the nose is not an impressive finding and could be easily overlooked, especially in those colleagues who never have heard of this entity, or they simply do not believe in something like that.

Because of that, both anterior rhinoscopy and fiber endoscopy, before and after the decongestion of nasal mucosa, showed no remarkable, glaring morphologic findings in terms of any particular edema of the nasal mucosa or abovementioned morphologic irregularities. Even more, the acoustic rhinometry findings in such patients are in rule within normal ranges as well as CT scans.

5.2 Clinical Appearance of the Cobweb Rhinitis

In all of the patients, there was one unusual clinical finding in the nose: almost transparent but still whitish, very delicate mucous filaments extending between the medial surfaces of the anterior thirds of the inferior turbinates on one side and septal mucosa of the corresponding region at the other side, resembling a cobweb (Figs. 5.5, 5.6, and 5.7). Once again, cobweb rhinitis is always located in the anterior third of the nasal cavity!

At the very beginning, i.e., at the time when we did not know anything about the cobweb rhinitis, the cotton swab samples have been taken for microbiological analysis from the very center of their cobweb-like nasal formations.

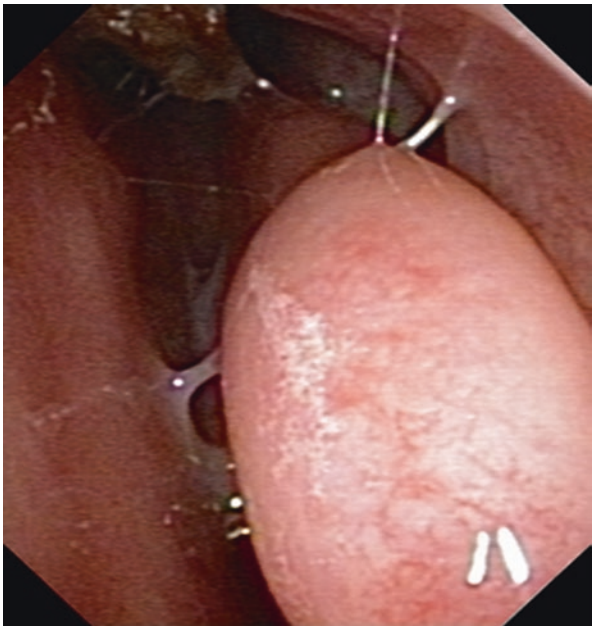

Fig. 5.5 A cobweb rhinitis of the left nasal cavity. The whitish, almost transparent filaments are stretched between opposite, neighboring mucosa surfaces, imitating in this way a cobweb

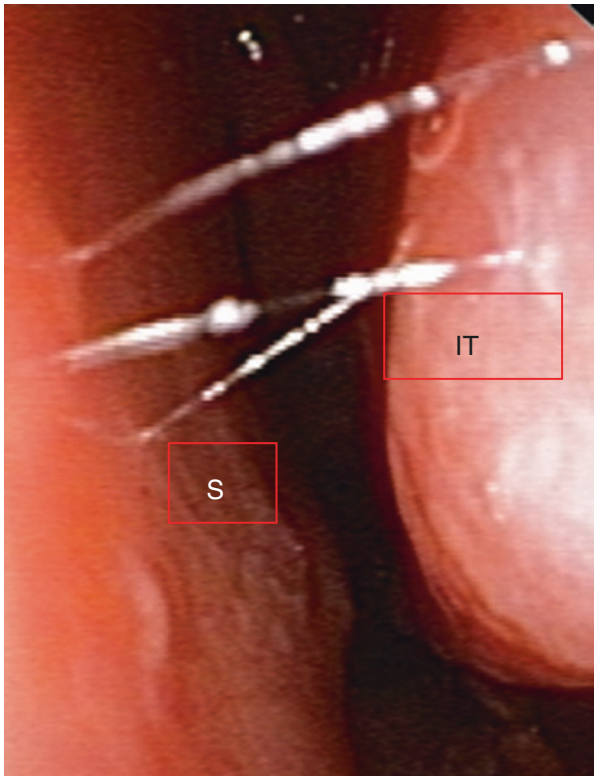

Fig. 5.6 A cobweb rhinitis in the left nasal cavity. *S* nasal septum, *IT* left inferior turbinate

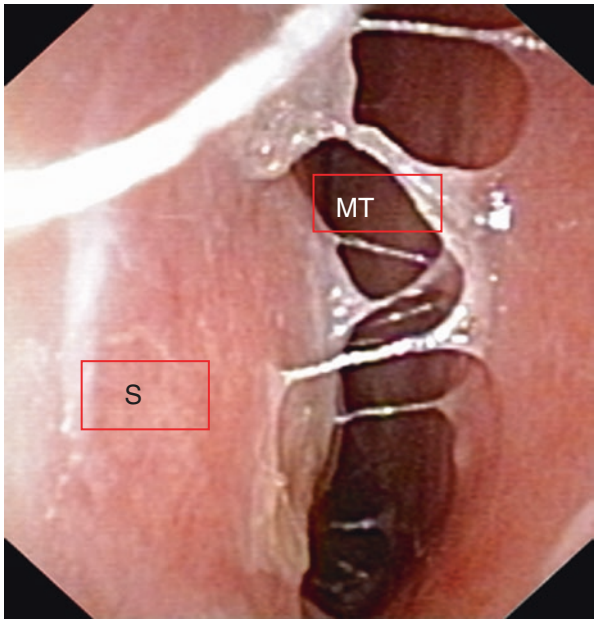

Fig. 5.7 Left-sided type 2 nasal septal deformty. *S* nasal septum, *MT* almost invisible, hidden left middle turbinate

Materials were planted on the Sabouraud agar (BBL Becton Dickinson and Company, New York, USA) modified 2% and the malt extract broth with gentamicin and colistin within 15 min at the latest. Samples were cultivated at 280 °C for 4 weeks. Identification was based on the microscopic and macroscopic characteristics of the mold colonies growing on the plates. The microscopic study involved direct examination of a small portion of each colony after addition of lactophenol cotton blue. Colonies in which no reproductive structure was identified were also examined in slide cultures.

Bacteria were not found in none of the samples after the usual 72-h period of incubation, and the finding thus has been considered microbiologically normal.

Fortunately, despite the fact that the analysis has been performed in one of the best microbiological laboratories, led by a very experienced, strict, and serious manager, miracle happened: one of the technicians just abandoned Petri plates with the material from the suspected noses, didn't put them in washing and sterilizing process, and gave in this way a chance for the colonies to grow undisturbed, forgotten, and abandoned for almost 24 days! Just by chance, as it often happens when discoveries are concerned, the next morning, the other technician found these abandoned plates and realized that something that resembles molds has grown over the agar (Fig. 5.8) and informed the manager about that. They immediately made photos of this finding and afterward analyzed them under the microscope.

They were extremely surprised to find out that the colonies belonged to the two families of quite newly discovered opportunistic fungi belonging to *Fusarium* and *Paecilomyces* species (Figs. 5.9 and 5.10)!

Fig. 5.8 The typical macroscopic appearance of the *Fusarium* colonies (white, oval-shaped colonies with a dark spot in the center—yellow arrows) and *Paecilomyces* colonies (colonies without the dark center—green arrows)

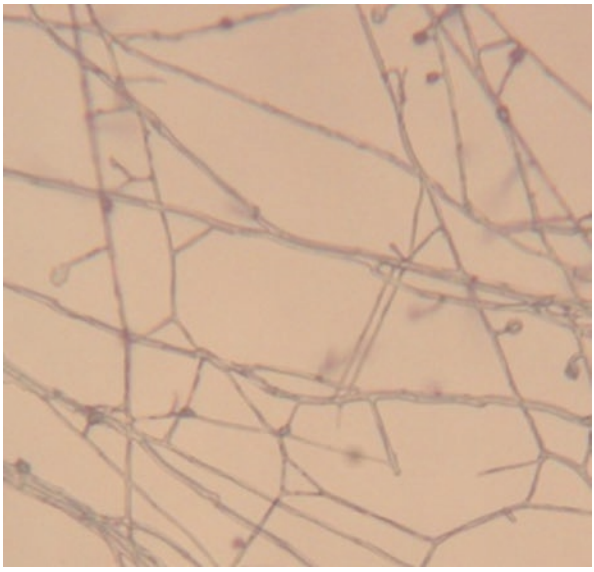

Fig. 5.9 Microscopic appearance of *Fusarium* (100×)

At that time, it was less than 10 years from the time when these two species of fungi have been identified as new potential pathogens for humans in general. *Fusarium* organism was isolated for the first time from millet grains in Kavango, Namibia, in the year 1985 and later on also in the Republic of South Africa and then from soil grassland near Emerald, Queensland, Australia, etc. This species has not previously been identified in plant or soil specimens in the Northern Hemisphere, nor has it been identified as a human pathogen at all! Anyhow, it is obvious that we are dealing with newly recognized microorganisms and this probably is the reason why the diagnosis of cobweb rhinitis has not been established earlier. Fungal infections have become known as an important cause of morbidity and mortality in recent

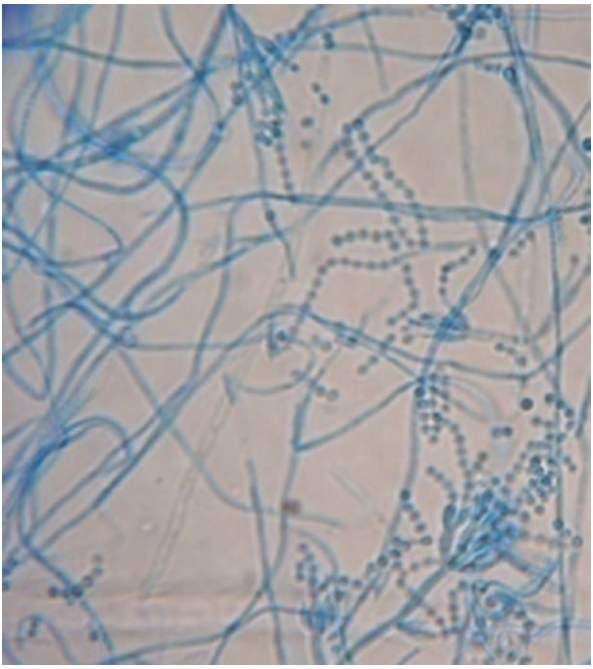

Fig. 5.10 Microscopic appearance of *Paecilomyces* (100×)

years, especially in the ever-expanding population of immunocompromised patients. Antibacterial treatment, bone marrow and solid organ transplantation, oncological chemotherapy, and primary or acquired immunodeficiency are all predisposing circumstances for the development of severe fungal infection. In addition to the traditional and well-known opportunistic fungi, such as *Candida*, *Aspergillus*, and *Cryptococcus*, many other fungi and molds have now emerged as causes of human infection.

Paecilomyces and *Fusarium* seem to be among them; they are considered as filamentous fungi but, at the same time, which sounds paradoxically, are of a particular clinical interest because of their resistance to antifungal agents! Some authors consider *Fusarium* and *Paecilomyces* soil saprophytes and important plant pathogens. *At the same time, they both have been recognized, step by step,* as agents of human mycosis.

Frequently, and this is most important, the infection is superficial. Deep tissue infection may occur as an opportunistic hyalohyphomycosis, whereas wide dissemination could be seen exceptionally in immunocompromised hosts. Members of the genus *Fusarium* are moniliaceous Hyphomycetes belonging to the class Deuteromycetes or Fungi Imperfecti of the order Moniliales.

Fusarium may be overlooked if cultures are not maintained as a smear on the plate for at least 3 weeks to permit the formation of characteristic microconidia (asexual, nonmotile spores of a fungus) and chlamydoconidia (result of asexual reproduction, forming conidia usually called chlamydoconidia). This fortunately happened to us, just by chance, as stated above.

Still, nowadays, among immunocompetent hosts, keratitis and onychomycosis are the most common infections caused by *Fusarium* and *Paecilomyces*. Less frequently, the infection may occur as a result of skin breakdown, such as burns and wounds, or the presence of foreign bodies, such as keratitis in contact lens wearers, which at times causes outbreaks of fusarial keratitis. Peritonitis in patients receiving continuous ambulatory peritoneal dialysis has also been described. Other infections in immunocompetent patients include sinusitis, pneumonia, thrombophlebitis, fungemia with or without organ involvement, endophthalmitis, septic arthritis, and osteomyelitis. But despite all of so numerous and well-documented anatomical locations mentioned above, there was no any report in the literature on *Fusarium* or *Paecilomyces* infection of the nasal mucosa! The first report has been given by Mladina in the year 2011. Mladina was the one to call this disease a cobweb rhinitis (arachnoidal rhinitis) and thus introduced for the first time a new clinical entity to the international rhinological audience.

Mladina also explained in detail the pathophysiology of cobweb rhinitis, including the consequences to the whole respiratory system based on the fact that the mycotoxins produced by *Fusarium* and *Paecilomyces* can suppress humoral and cellular immunity and cause tissue breakdown because of the excretion of the specific mycotoxins. In case of *Fusarium*, it goes for *fumonisins* and *trichothecenes*, whereas in case of *Paecilomyces* it is simply about *paecylotoxins*. Why do these specific mycotoxins play so important role regarding the nasal mucosa? They act against the normal function of the cogs of the branches of two important nasal mucosa nerves: nasopalatine and nasomaxillary nerve branches (both belonging to the trigeminal nerve). How do the mycotoxins act in human nose? They simply anaesthetize the cogs of the nasopalatine and nasomaxillary nerve branches, and the final effect is anesthetized nasal mucosal nerves. In such circumstances, the very beginning of the nasothoracal reflex is switched off! It is, otherwise, normal that the action potentials travel throughout the nasopalatine and nasomaxillary nerves to the trigeminal nerve nucleus located deep in the medulla oblongata. There, they have dense connections (anasthomoses) with the nuclei belonging to the cervical nerve plexus. One of the nerves that rise from the cervical plexus is a phrenic nerve. Furthermore, for the normal and sufficient contraction of the diaphragm, the phrenic nerve action potentials are strictly required. The sufficient contraction of diaphragm means a deep pulmonary breathing. Now, if the beginning of the nasothoracal reflexes (the cogs of the nasopalatine and nasomaxillary nerves) is "switched off" because of anesthetic effect of mycotoxins, both from *Fusarium* and *Paecilomyces* molds (cobweb rhinitis), the nasothoracal reflex does not function well, and the pulmonary breathing becomes shallow, i.e., of a non-diaphragm type. In other words, pulmonary function tests show restriction, which may be moderate to severe (30–50% predicted total lung capacity) in bilateral diaphragmatic paralysis. The restriction worsens when supine, evidenced by a drop in vital capacity of 30–50% in bilateral diaphragm paralysis. This test is sensitive and has a high negative predictive value: if there is no reduction in FVC when supine, there is probably no significant diaphragmatic paralysis.

The incidence of infections with both *Fusarium* and *Paecilomyces* in immunocompetent hosts is increasing! One should not forget that *Paecilomyces* can be

recovered from soil and air and can cause the deterioration of grain, food, and paper. *Paecilomyces* species' potential resistance to sterilizing methods, their frequent contamination of creams and lotions used clinically, and their colonization of clinical materials, e.g., catheters and plastic implants, increase the clinical importance of this fungus. Although *Paecilomyces* species are still generally considered as uncommon pathogens in man, it should be emphasized that the incidence of such infections even in immunocompetent hosts is increasing! This means that rhinologists must keep an eye on this new clinical entity in their future everyday practice!

5.3 The Treatment of the Cobweb Rhinitis

At the end of the day, the question arises about the treatment of the cobweb rhinitis. It is very simple: mechanical removal of the cobweb elements by means of vigorous nasal irrigation. The best results have been achieved so far by aqueous nasal sprays (sterile seawater, physiologic solutions, etc.) which should be applied to the nasal cavity approximately five to six times a day. The aim of this treatment is literally to remove all the elements of the cobweb formations, even those invisible by the naked eye. The treatment should last for 3 weeks at least, with no exceptions. One of the most important factors for the success of the treatment is patient's true understanding of the disease, its nature, and the consequences for the respiratory system in general. Patients usually expect some medication; according to the people in their closest surrounding, the doctor might have forgotten to prescribe also an antifungal medication since they have been told that there is some special kind of fungi, in fact nasal molds, in their nasal cavities. The doctor should, therefore, explain to the patient in advance that these microorganisms do not respond to any of the known antifungal drugs.

The control nasal mucosal smear should be sent to the microbiological laboratory with the obligatory remark that it is from a cobweb rhinitis patient who is under therapy. This will be the signal to the colleagues in the lab to cultivate the smear and let the Petri plate stay for at least 4 weeks as to see whether or not any mycotic or mold colonies grow. In case there was not a clear remark about the diagnosis, it could happen that the doctor receives negative microbiological results since no bacteria have been found to grow on the plates after the usual bacteriological time: 72 h!

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What Is Honeymoon Rhinitis?

6

Murat Koçyiğit, Nuray Bayar Muluk, Gordon Soo, and Jeffrey C. Bedrosian

6.1 Introduction

Sneezing is an action whereby air is convulsively expelled from the lungs via the oral and nasal cavities. The action is typically precipitated by irritation of the lining of the nose by foreign particles and is usually only under partial voluntary control. Histamine is released in response to the particles, and this activates a reflex involving cranial nerve V [1].

The ventromedial portion of the spinal trigeminal nucleus, together with the nearby lateral reticular formation in the pons and medulla, is the neuroanatomical regions responsible for sneezing. These areas apparently control several groups of muscles which work together to produce sneezes: those in the pharynx, those within the larynx proper and the muscles of respiration [1].

Sexually induced sneezing is not triggered by irritation of the nasal cavity nor by allergenic stimulation. It may happen at any stage during sex. One term to describe the phenomenon is "honeymoon rhinitis" [1]. Honeymoon rhinitis thus refers to the situation where sexual activity leads to nasal symptoms, including sneezing, running and stuffiness (i.e. congestion) [2].

There are a number of ways in which an acute exacerbation of asthma may be brought on, such as acquiring an infection, exposure to allergens, exertion or

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_6

psychological stress. There are infrequent reports of sexual intercourse setting off asthma attacks or rhinitis episodes [2–4]. A first experience of sex may bring an association of sex with asthma, as Strauss and Dudley identified [5]. Despite the known association of exertion with rhinitis in some people, for the cases where sex had triggered the episode, exertion in the form of an exercise tolerance test or climbing two flights of stairs failed to reproduce the symptoms. The conclusion is, then, that sexual arousal, rather than exertion, was the triggering cause for rhinitis following intercourse [2].

There are reports within the literature of women becoming allergic to allergens contained within seminal fluid, and this then triggers asthma after sexual contact [6]. Monteseirin et al. [2] state that their cases of women with rhinitis following coitus showed no signs of systemic or localised allergy and did not have a positive titre for specific IgE to semen (HYCOR 288) and using a condom had no effect on the symptoms. Cutaneous prick testing (Bial-Aristegui) and specific IgE titre for latex were both negative. Honeymoon rhinitis occurred even when condoms were not used.

6.2 Epidemiology

Precise estimates of how prevalent hypersensitivity responses are in the context of sexual activity are lacking. Nonetheless, such responses clearly exact a heavy toll on the life quality and sexual enjoyment of those affected. A range of allergic conditions have been discovered to impair sexual enjoyment [7], including asthma, rhinitis, urticaria and allergic eczema, in addition to allergies to foodstuffs, latex and medications.

Potentially, honeymoon rhinitis may be present in both males and females for their whole lives, but patient reticence about mentioning bizarre and embarrassing symptoms to their clinician results in under-reporting. Internet chat rooms and forums are often valued for their anonymity, and in such places the symptoms may be more readily disclosed [1].

6.3 Mechanism

Sexual activity per se may set off a hypersensitivity reaction, or allergens may therefore be transferred. Allergens found in food or medication may be transferred via body fluids, such as semen or saliva. Condoms contain latex, which may be allergenic, and there are multiple potential allergens found in lubricants, spermicides, topical drugs and cosmetic products. Sexual behaviour per se is important in the aetiology of allergic responses within the respiratory tract, such as honeymoon asthma or honeymoon rhinitis. Proteins found in semen are the allergens responsible for hyperreactivity to seminal plasma [7].

Precisely how coitus triggers honeymoon rhinitis is unknown, but psychological aspects (both arousal and fear) might be responsible, rather than simply the physical exertion involved in having sex [8]. The autonomic system plays a role in the sexual response, especially as orgasm approaches, when the parasympathetic autonomic

response is dominant. Strong emotional feelings associated with sexual activity may intensify [8] autonomic disequilibrium [4]. It is known that mast cell degranulation may be triggered by acetylcholine release at nerve terminals, which may help explain what is happening during an episode of honeymoon rhinitis [9].

There seems to be a genetic predisposition to honeymoon rhinitis. The nose contains tissue that is capable of tumescence. Autonomic activity that causes genital tumescence in both males and females may also cause engorgement of nasal erectile tissue [10]. Indeed, a known adverse effect of sildenafil citrate is congestion of the nose, which likely represents a similar mechanism in action [11].

Thus, autonomic disequilibrium, with cholinergic predominance, potentially resulting from the physiological and psychological aftermath of coitus, may explain how honeymoon rhinitis actually presents. The onset of symptoms varies widely—from during foreplay to 6 h after intercourse. The symptoms vary on a spectrum from mild, with spontaneous resolution, to severe, with the need for respiratory support. It has been proven that taking an inhaler containing a β_2 agonist, in conjunction with a steroid inhaler or nasal cromolyn, is beneficial in prophylactically stopping the condition [7].

There are three theories to account for honeymoon rhinitis, of which the last mentioned has the most support [1]:

1. Psychological theory. The sneeze may be seen as a powerful way of indicating sexual release. This explanation suffers from the drawback that it suggests sneezing is under voluntary control, which is not the case [1].
2. Humoral factor theory. This explanation posits that nitric oxide is transported in the circulation, leading to genital engorgement, and that the nasal erectile tissue responds to the circulating nitric oxide. The drawbacks to this theory are as follows: (a) The timing of events is wrong, and (b) nitric oxide release that causes penile erection is a localised event and is not associated with significant levels of circulating nitric oxide [1].
3. Parasympathetic activity theory. The rapidity of the rhinitis response is more likely to imply nervous system participation than endocrine activity alone [1].

6.4 Clinical Studies

It was already acknowledged that sexual activity per se can set off the symptoms associated with respiratory allergic disorders. Symington and Kerr [12] used a new term, "sexercise-induced asthma," in their 1976 description of dyspnoea and wheezing in the context of intercourse in cases of known exercise-related asthma. More recently, however, there has been recognition that honeymoon asthma and honeymoon rhinitis are not simply exercise-related—the pathophysiology being different [3]. Indeed, not only did walking up two flights of stairs (which equates to the effort needed for coitus) not reproduce symptoms in the upper or lower airway in cases of honeymoon rhinitis/asthma [3], but honeymoon rhinitis/asthma was also found to exist even where no other history of asthma or rhinitis was discernible [13].

A study performed in Turkey in 2005 looked at 43 individuals with allergic rhino-conjunctivitis (ARC). Uncontrolled ARC was associated with worse scores on the Female Sexual Function Index and the International Index of Erectile Function than either asymptomatic ARC cases or healthy controls. For men, treating the symptoms affecting the conjunctivae and nose led to an improvement in all the indices of sexual function. Women who were treated adequately reported desiring sex more, becoming more aroused and having better orgasms. Treatment did not improve vaginal lubrication, enjoyment of sex or reduction in pain [14]. A US-based study dating from 2009 also revealed an impairment on sexual functioning in sufferers from ARC [15]. The study used the Rhinosinusitis Disability Index (RSDI), which has a question concerning sexual activity. Of the individuals surveyed, 55.9% admitted that ARC had a negative impact on sexual functioning, at least some of the time. ARC had a worse effect on sexual function than nonallergic rhinitis. Healthy controls scored better than ARC cases for this item, too.

A cohort-based study examining 365 cases who presented to accident and emergency, and consisting of 228 female and 137 male asthma sufferers, found that 58% experienced impairment in sexual functioning due to asthma. The researchers discovered the risk factors contributing to sexual impairment. They were moderate or severe asthma, being female, being at least 40 years old, earning less, having been exposed to indoor mould and having been exposed to mice. The mean odds ratios were (with corresponding 95% confidence interval shown in parentheses) 2.5 (1.5–4.2), 1.6 (1.0–2.7), 2.7 (1.6–4.3), 2.0 (1.1–3.6), 3.6 (1.7–7.5) and 1.8 (1.1–3.0), respectively. It was noteworthy that sexual function was cited as the third most common area of life in which sufferers experienced restrictions. Climbing stairs and housework were the two most common complaints [16]. A Dutch study dating from 2008 [17] examined the sexual life of 30 asthma and 25 COPD patients and compared them with healthy individuals. The scales used were the Intimate Physical Contact Scales and the Respiratory Experiences with Sexuality Profile. Although the asthma sufferers had a better sexual life than the COPD sufferers, both groups fared worse than the healthy controls. Both men and women in the patient groups complained of a loss of desire. Women patients (but not men) complained of less satisfying orgasms and lower self-esteem [17].

6.5 Treatment

It has been reported that beclometasone nasal spray improves and may abolish symptoms of honeymoon rhinitis. Cromolyn nasal spray alone has been shown to lack efficacy in honeymoon rhinitis [2, 3].

6.6 Conclusion

To summarise, autonomic disequilibrium, with cholinergic predominance, potentially resulting from the physiological and psychological aftermath of coitus, may explain how honeymoon rhinitis actually presents. Symptom onset varies, from

during foreplay to 6 h after intercourse. The symptoms may be mild and resolve spontaneously, may be severe and result in the need for respiratory support or anywhere in between. It has been proven that taking an inhaler containing a β_2 agonist, and in conjunction with a steroid inhaler or nasal cromolyn, is beneficial in prophylactically stopping the condition [7].

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Recurrent Epistaxis from Kiesselbach's Area Syndrome (REKAS)

7

Ranko Mladina

7.1 Introduction

Vascular diseases are a major threat to human health nowadays. Cardiovascular diseases, including coronary heart disease and a stroke, are the leading cause of death in the United States and Europe. Several risk factors (i.e., stressful life, overweight, physical inactivity, smoking, hypertension, and diabetes mellitus; high levels of cholesterol and lipids; and, so far only hypothetically, the genetic predisposition to the development of the acute coronary syndrome because of certain deletion of some of the chromosomes that causes both the development of some of the dominantly inherited types of nasal septal deformities, i.e., types 5 and 6) are associated with the development of cardiovascular disease. Hypertension and cardiovascular disease, including atherosclerosis, cardiac hypertrophy, and ischemic disease, nowadays have been increasingly recognized as inflammatory diseases. In recent years, this hypothesis has led to heightened interest in studying the role of inflammatory cytokines in the pathogenesis of this diseases. Like arteries, the veins are also a part of vascular system and have their own pathology.

Varicose veins are tortuous, twisted, or lengthened veins. The theory that varicose veins result from failure of valves in the superficial veins leading to venous reflux and vein dilatation has been superseded by the hypothesis that valve incompetence follows rather than precedes a change in the vein wall [1]. Thus, the vein wall is inherently weak in varicose veins, which leads to dilatation and separation of valve cusps so that they become incompetent. Risk factors for varicose veins include increasing age and parity and occupations that require a lot of standing.

Hemorrhoids are a very widespread disease causing pain by thrombosis, fear by bleeding and burden by weeping and itching. Hemorrhoids occur when the external hemorrhoid veins become varicose (enlarged and swollen), which causes itching, burning, painful swellings at the anus, dyschezia (painful bowel movements), and

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_7

bleeding. Pain with bowel movements and bleeding are often the first signs of hemorrhoids. It was Taweevisi and his team who proposed that mast cells have a multidimensional role in the pathogenesis of hemorrhoids, through the actions of the chemical mediators and cytokines released from mast cell granules [2]. Some investigation focuses on caliber and flow changes of the terminal branches of the superior rectal artery supplying the corpus cavernous recti in patients with hemorrhoids.

The role of inflammatory cytokines in the pathogenesis of these diseases is very important. The lamina propria in the nasal mucosa is rich in blood vessels and humoral mediators. Vascular diseases are a major threat to human health nowadays. Cardiovascular diseases, including coronary heart disease and a stroke, are the leading cause of death in the United States and Europe. Several risk factors (i.e., stressful life, overweight, physical inactivity, smoking, hypertension, and diabetes mellitus; high levels of cholesterol and lipids; and, so far only hypothetically, the genetic predisposition to the development of the acute coronary syndrome because of certain deletion of some of the chromosomes that in such patients causes both the development of some of the dominantly inherited type of nasal septal deformities, i.e., type 5 or type 6) are associated with the development of cardiovascular disease. Hypertension and cardiovascular disease, including atherosclerosis, cardiac hypertrophy, and ischemic disease, nowadays have been increasingly recognized as inflammatory diseases. In recent years, this hypothesis has led to enlargement of interest in studying the role of inflammatory cytokines in the pathogenesis of these diseases.

7.2 Are There Any Predisposing Factors for the Onset of REKAS?

It seems there are at least three predisposing factors for the development of REKAS. The leading factor could be the existence of emphasized structure of the main venous plexuses in the particular organism. That could explain why anterior nose bleeds are not that frequent despite the fact that all human beings have it in their noses. Secondly, perhaps local mechanical reasons could contribute to the further enlargement of the particular vein branches within Kiesselbach's plexus itself like anterior nasal septal deformities are. It regards exclusively to types 1, 2, and 6 as anterior septal deformities, placed almost exactly where Kiesselbach's plexus is located. The vertical deflections of the anterior septum in types 1 and 2 could cause locally uptight veins and in this way make them less elastic. Finally, the trigger moment for the onset of the nose bleed could be the inflammation of the skin covering the nasal vestibule and Kiesselbach's plexus. The inflammatory cytokines could contribute to the microruptures of the venous wall within the plexus itself, and the bleeding can start. Recurrent epistaxis (nose bleeds) from Kiesselbach's area syndrome (REKAS) was first mentioned as early as 1985. It has been found that 90% of patients suffering from recurrent nose bleeds from Kiesselbach's area simultaneously suffered from hemorrhoids. Clinical observations suggest a possible mutual pathophysiologic relationship between Kiesselbach's and anorectal venous plexus.

This relationship is also suggested in the reverse direction: significantly more than two thirds of primarily hemorrhoid patients (83.01%) showed simultaneous vascular dilatations within their Kiesselbach's plexuses, but none of these patients had ever had recurrent nose bleeds. There is one more thing they did not have (contrary to REKAS group): anterior septal deformity. Furthermore, REKAS and hemorrhoid disease, despite being different clinical entities, frequently appear in the primarily REKAS patients or their closest relatives (more than 90% out of all!). At the same time, all of REKAS patients did have a certain degree of the anterior septal deformity, which primarily hemorrhoid patients did not have at all.

One should not forget the importance of the local bacterial inflammation. In REKAS patients, the leading bacteria found is *Staphylococcus aureus*. Since Kiesselbach's plexus is covered by skin as is the whole nasal vestibule, it suggests inflammation of the whole vestibule and was thus called "vestibulitis nasi."

It is generally presumed that Kiesselbach's vascular plexus in Little's area (Figs. 7.1 and 7.2) of the nasal septum belongs to the same group as anorectal venous plexus (Fig. 7.3) does (others of this group are brain, esophagus, and lower leg venous system).

Sporadic nose bleeds, mostly unilateral, are the most frequently seen nose bleeds in everyday practice. In most of the cases, the patients are used to short episodes of bleeding and are almost trained how to stop it by themselves. It goes for the bleeding from the venous plexus located very anterior at the nasal septum. Sometimes even venectasies can be found in the plexus area, particularly in elders. The bleedings from this area are simple to manage, and because of that they do not attract particular attention among rhinologists. But, time and again, it becomes obvious that the nose, from its really very anterior part, can play a role of the specific mirror of what lies behind the "pathology" that can be diagnosed easily. The modern rhinologist should know that behind this relatively easy-to-solve problem almost always lies something that the patient should be warned about for the future.

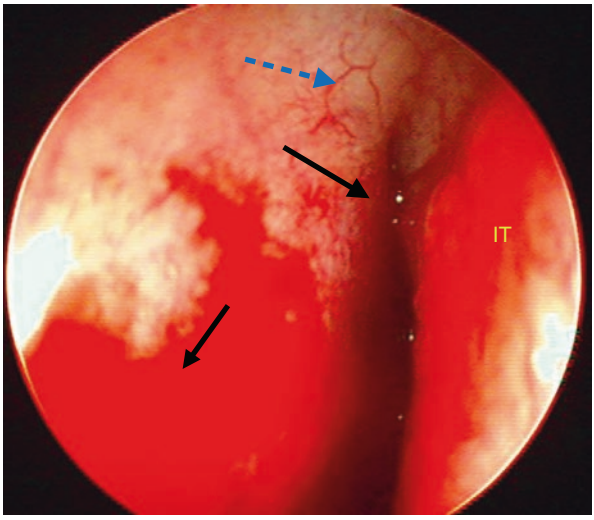

Fig. 7.1 Left nasal cavity. Typical appearance of an acute nose bleeds from Kiesselbach's area. S—nasal septum showing a slight left-sided type 1 deformity (black arrow). IT—inferior turbinate shows some traces of the bleeding in the closest neighborhood. The dilated veins of Kiesselbach's plexus can be easily identified (dotted blue arrow)

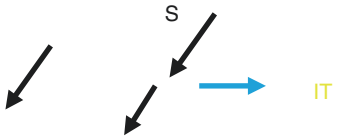

Fig. 7.2 Left nasal cavity. Intermaxillary bone wing (white star). Note the vascular network and some tortuous branches (black arrows) in Kiesselbach's area. *S* nasal septum, *IT* inferior turbinate. Dotted white arrow indicates the septal groove which undoubtedly indicates type 6 nasal septal deformity. Besides, the left-sided type 2 deformity in this very case is obvious as well (dotted blue star)

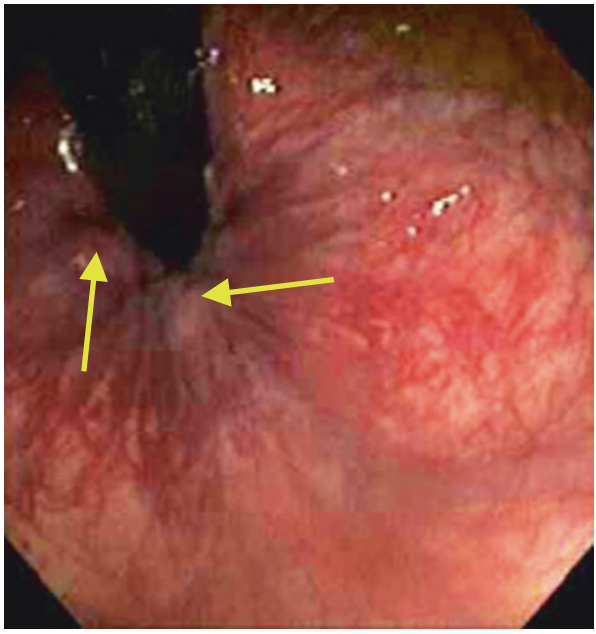

Fig. 7.3 Typical appearance of the anorectal hemorrhoid disease. Two notches of the dilated veins can be easily identified here (yellow arrows)

For instance, the bleeding from Kiesselbach's venous plexus requires checking up of the blood pressure, regardless whether it goes for a pediatric or adult patient. Clinical experience showed that particularly elevated values of the diastolic blood pressure contribute to the start of bleeding.

However, it seems that much more important fact connected to REKAS is that Kiesselbach's venous plexus is just one of the five venous plexuses in human body that has almost the same structure, although not of the same size neither the diameter of the veins that constitute them. So, besides Kiesselbach's plexus, there are almost the same venous plexuses in the anal region, within the brain veins, esophagus, and the lower legs. That is why in most of the REKAS patients, particularly in adult ones, there are positive anamnesis data about hemorrhoid disease in the patient himself or herself, dilated veins of the lower legs, strokes in older members of the blood-related family, and, rarely, the diseases that include esophageal bleeding.

7.3 Some Pathophysiological Aspects of the Nasal Blood Vessels

Large venous cavernous sinusoids, mainly localized in the inferior turbinates, are characteristic of nasal mucous membrane. It is possible that Kiesselbach's venous plexus belongs to the same group but is not covered by nasal mucosa. It is covered, as stated above, by vestibular skin!

The lamina propria in the nasal mucosa is known as rich in blood vessels. The arterioles are conspicuous by an absence of internal elastic membrane. Porosity of the endothelial basement membrane is a characteristic of nasal blood vessels. The question arises here whether or not some hereditary moments could influence this system taking into consideration the fact that in very many of REKAS patients coexisting problems with anorectal diseases were found.

The extravasations of plasma through the walls of postcapillary venules take place during inflammation of the mucosa or the tiny skin covering the nasal vestibule. The process runs through the gaps in the intercellular junctions between the endothelial cells. This leads to an increase of the interstitial liquid volume and pressure, which, in addition, tends to force transfer of plasma-like liquid as an exudate. The humoral mediators that cause extravasation of plasma are many and include histamine, bradykinin, various prostaglandins, and sensory nerve neuropeptides such as substance P. In certain moment, they could shift to a real bleeding instead of extravasation of plasma exclusively.

7.4 Recurrent Epistaxis from Kiesselbach's Area and Anorectal Venous Plexus: Do They Have Anything in Common?

Nose bleeds, whether spontaneous or otherwise, are experienced by up to 60% of people in their lifetime, with 6% requiring medical attention [3]. The etiology of nose bleeds can be divided into local and general causes; however, most (80–90%) are actually of unknown etiology [4].

Recurrent nose bleeds from Kiesselbach's area syndrome (REKAS) was first mentioned as early as in 1985 [5]. This syndrome was found to be the result of a simultaneous interaction between the following four constant factors: (a) specific anterior nasal septal deformity, (b) dilated vessels of Kiesselbach's venous plexus, (c) infection of the nasal vestibule skin, and (d) heredity.

Regarding hemorrhoid disorders, a large number of REKAS patients, i.e., 90% of them, were found to suffer from hemorrhoids. Local chronic infection was suggested to be a causative factor for both hemorrhoids and REKAS patients. Furthermore, the symptoms of hemorrhoid diseases (and also of varices cruris, cerebral strokes) were found in the closest relatives of 90% of REKAS patients or even in themselves, strongly suggesting a hereditary predisposition for venous plexus disorders, as is the case with hemorrhoids. This relationship, however, as to the hemorrhoid disease, also exists in the reverse direction: more than two thirds of

primarily hemorrhoid patients showed simultaneous vascular dilatations within Kiesselbach's plexus (83.01%). However, none of these patients had recurrent nosebleeds. This suggests that vascular dilatations within Kiesselbach's venous plexus are not per se an exclusive, crucial factor for the onset of nose bleeds.

Thus, the question arises here about which additional factors were missing as to produce the onset of recurrent nose bleeds from Kiesselbach's plexus also in our primarily hemorrhoid patients: anterior septal deformities (types 1, 2, and 6 or a combination of previous), vestibular infection, or perhaps both. However, anterior septal deformities showed a very low incidence (7.5%) in hemorrhoid patients, whereas the signs of a slight vestibular infection were also very rarely found (3.8%) in this group. Since neither vestibular infection nor anterior nose bleeds from Kiesselbach's plexus appeared in primarily hemorrhoid patients despite dilated vessels in their Kiesselbach's venous plexuses and a positive hereditary factor, it is generally believed that this situation was due to the absence of the anterior septal deformity in these patients at the first place.

Finally, it could be stated that Kiesselbach's vascular plexus belongs to the group of affine venous plexuses in the body (brain, esophagus, anorectal region, and lower leg venous system). Further, a long-lasting distension of Kiesselbach's plexus veins, coming from below due to the anterior septal deformity (types 1, 2, and 6 or combinations, all of them anteriorly positioned), could be the influential predilecting factor for the onset of an inflammation of the nasal vestibule. Finally, the inflammation itself overtakes the main role: it could be a trigger for the start of the anterior nose bleed recurrences. *Staphylococcus aureus* was identified in bacteriological smears from the nasal vestibule of REKAS patients in even 93%!

7.5 How to Treat Nose Bleeds in REKAS Patients?

First of all, there should be a precise diagnostic procedure performed, regardless of panic which usually is present both in patients themselves and sometimes in young doctors on duty as well. First of all, the value of the blood pressure has to be evaluated. In cases of hypertensive crisis, the internal medicine doctor should be consulted. The doctor should not forget to ask the patient about any continuous drug therapy, particularly in sense of antihypertensives, acetylsalicylic acid tablets, etc. Anyhow, the patient should be encouraged and gently asked to blow the nose, side by side, as to remove all the clogs and bloody secretions from both nasal cavities. The patient should be informed that nothing bad is going to happen if he or she blows the bleeding nose! It is quite usual that patients do not believe the doctor; they are simply scared and afraid. Immediately after that, the doctor should apply at least two puffs of nasal decongestive spray in both nasal cavities and close the patient's nose tightly by his (doctor's) fingers. The patient should be given ice cubes to keep them in the mouth, leaned at the hard palate. Cooling the hard palate helps a lot to get local vasoconstriction in this region and thus in very many cases of nose bleeds diminish the intensity of bleeding or even temporarily stop it. On the other side, patients get involved in the treatment as an active partner and get more and more

confident which is extremely important. If the patient is not motivated to collaborate, he or she will be passively sitting down just as an object, waiting to be treated and retrieved, nothing else. After a few minutes of puffing the nasal decongestant in the nose, the doctor takes another look into the cavities. In case it obviously doesn't go for REKAS, but the nose bleed seems to come from deeper parts of the nose, several puffs of local anesthetic should be applied bilaterally as to enable smooth passing of the nasal fiber endoscope up to the sphenopalatine region. In this way, the doctor can get clear clinical information about the location of the bleed source: does it come from deep(er) parts of the nasal cavity, and is the bleeding unilateral or bilateral? During the maneuvers with the patient's nose, the doctor should ask about any kind of recent trauma against the nose (including picking of the nose which otherwise is very common in cases of inflammation of the nasal vestibule). If it goes for anterior bleeding from Kiesselbach's area, various tools could be used to stop active bleeding, depending on how equipped is the doctor's office: the source of bleeding can be "weld up," be it by means of chemical solutions (like 5% up to 20% solution of the silver nitrate, $AgNO_3$) applied on the top of the cotton swab, touching gently the source of bleeding, monopolar or bipolar electrocoagulation, or some of the lasers (for instance, the CO_2 laser). In rule, cauterization is not painful and does not require any anesthesia.

After the bleeding is stopped, a piece of antibiotic cream (about 1 cm long) should be applied right into the top of the nasal vestibule, i.e., at the junction between the limen nasi (anterior nasal valve) and the nasal septum, and then the small gauze tampon should be inserted into the nasal vestibule. The vestibular packing should be bilateral in all cases, regardless of the fact that the bleeding was unilateral only.

The patient should be prescribed an antibacterial drug for 5 days' peroral use. The fifth day after the intervention, the patient comes for the extraction of the package and the control.

In case the patient has septal deformity of types 1, 2, and 6 or some combination of the previous, he or she would be strongly recommended for the septal surgery in the closest future. This happens in about 6% of all REKAS patients.

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Local Allergic Rhinitis: A New Allergic Rhinitis Phenotype

8

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8.1 Introduction

Local allergic rhinitis (LAR) describes a condition in which a patient has clear symptoms suggestive of allergic rhinitis and has a nasal eosinophilic inflammation with local specific IgE to a specific allergen but is negative on testing for systemic atopy [1].

Huggins and Brostoff first demonstrated local production of specific IgE antibodies in allergic rhinitis patients with negative skin prick tests [2]. In 2003, Powe introduced the concept of "entopy" [3] to indicate allergic sensitization confined to the nasal mucosa, without systemic sensitization. Rondón et al. were the first to propose LAR as an entity, after reviewing all the data that were available about the condition [1]. They had demonstrated that 54% of individuals who supposedly had symptoms of nonallergic rhinitis (NAR) on the basis of negative tests (SPT and serum sIgE) did, in fact, respond positively to NAC with *Dermatophagoides pteronyssinus* [4]. A follow-up study of 10 years of evolution undertaken by the same researchers in a cohort of 176 individuals with LAR and 115 healthy controls showed that LAR patients experienced a clinically relevant and statistically significant worsening on their rhinitis symptoms, with negative impact on their quality of life. It is noteworthy that 9.7% of LAR cases went on to develop AR (the disease became systemic, in other words). The corresponding rate for controls was 7.8% ($p = 0.623$). These results point to LAR being clearly a separate disorder in its own right and to a tendency for it to worsen over time [5].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_8

A considerable number of cases with rhinitis, in which SPT is negative and sIgE is undetectable, do in fact produce a positive response to the nasal allergen challenge (NAC). This phenotypical manifestation of AR is known as LAR. LAR affects the entire age range from children to adults, across the world, and symptoms may range from mild to severe. Despite the negative effects of LAR on patients' quality of life and the way symptoms may quickly deteriorate, it is generally underdiagnosed. LAR persists as a condition in its own right. It is not merely a precursor to systemic AR. There are many common elements between AR and LAR, such as positive NAC, the presence of features indicating a type 2 inflammatory response in the nose (e.g. sIgE in secretions from the nose) and an increased risk of becoming asthmatic [6].

8.2 Epidemiology

Different studies evidenced that LAR is an underdiagnosed entity, affecting a considerable proportion of non-atopic rhinitis individuals of different countries, ethnic backgrounds and age ranges, as is been recently documented by Eguiluz-Gracia et al. [7]. Although the exact prevalence of LAR in the general population is unknown, the prevalence study performed in 2012 by Rondón et al. [8] in a group of 428 adult patients with rhinitis found that 25.7% fulfilled the criteria for LAR compared to 63.1% with AR and 11.2% with NAR. In both allergic phenotypes (AR and LAR), the most frequent source of the allergen was *D. pteronyssinus*. A study of 219 elderly (average age 65.8 years) individuals identified 21% as suffering from LAR and 40.2% from AR. Not only are these figures similar to the 2012 study, but they also identified *D. pteronyssinus* as the major source of the allergens responsible [9].

A recent systematic review from Hamizan et al. including data from 3400 patients and healthy controls reports a similar prevalence data of LAR with a 24.7% probability of a positive NAC in rhinitis patients testing negative for both SPT and serum sIgE [10].

These are the frequencies in patients already known to have rhinitis, but they cannot tell us what prevalence to expect in the general population, for which epidemiological surveying will be necessary.

8.3 Mechanisms

The pathophysiology of AR depends on an immediate IgE-mediated immunological reaction to environmental allergens including an early-phase response due to IgE-mediated mast cell degranulation and mediator release and a late-phase response with recruitment of eosinophils, basophils and T cells expressing a T2 cytokine profile, as interleukins 4 and 5. It has now been discovered that three other cytokines are important in regulating the Th2 response: thymic stromal lymphopoietin, interleukin 25 and interleukin 33 [11]. The pathogenesis of LAR is only partially

understood. However, similar to AR, nasal mucosa of LAR patients shows a T2 allergic inflammatory response to aeroallergens (increased levels of eosinophils, mast cells and T cells), including an early-phase response with nasal production of mast-cell mediators as tryptase and a late-phase response with nasal production of eosinophilic cationic protein (ECP) [12].

8.4 Diagnosis

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The initial approach diagnosing LAR should always include a detailed clinical history and a nasal endoscopy or sinus CT scan to rule out chronic rhinosinusitis or anatomical disorders. The next step should be the evaluation of the allergic response at the target organ performing a NAC. The NAC is the gold standard for LAR diagnosis, and nasal sIgE and the basophil activation test (BAT) are also beneficial in reaching a diagnosis [13, 14]. Whilst the traditional management of LAR cases calls for avoidance of the specific allergen, coupled with histamine blockers and intranasal steroid therapy, specific allergen immunotherapy (AIT) has now been shown to be efficacious and safe in treating allergies to grass pollen [15] and *D. pteronyssinus* [16].

NAC helps to distinguish allergic disorders (AR and LAR) from nonallergic disorders (NAR) or the absence of disease. It can also reveal the culprit allergen in AR patients with multiple sensitization in SPT or serum sIgE [10, 17]. It is advised that a nasal saline instillation test be performed prior to NAPT to exclude the patients having non-specific hyperresponsivity in the nasal region [2, 13, 15, 16, 18–22].

NAC has high levels of sensitivity, specificity and reproducibility but takes time to perform and necessitates trained healthcare personnel to carry it out. A modified version of NAC with multiple allergens in the same session (NAC-M) has reduced the number of visits [21]. Recent results show that LAR cases will respond to purified allergens, as do cases of AR. Of individuals with LAR, 83% show reactivity to nOle e 1 [23].

The nasal sIgE determination sensitivity for diagnosis of LAR is low (positive in 20–43%) of LAR cases [24–28]. To measure nasal sIgE, several samples have been used (secretions, scraping, brushing, tissue homogenates, etc.) [25]; recently, all of them cannot be applied to LAR. Therefore, nasal sIgE should be considered a research tool; mainly, it cannot be recommended for routine diagnosis of LAR [7, 29–31].

BAT is a different diagnostic method in LAR whose performance has been investigated. Of HDM-LAR patients, 50–53.3% have been reported to show positive BAT responses according to different group studies [32, 33]. Importantly, IgE-dependent activation of basophils was confirmed in wortmannin experiments [33]. A 66.6% sensitivity of BAT was reported for the diagnosis of "*Olea europaea*-LAR patients" [34]. The NAC is the basis for diagnosis of LAR; however, nasal sIgE and BAT should be considered mainly as research tools [7].

8.5 Clinical Features

It has been noted by Rondón et al. [5] that LAR tends to worsen over 10 years, a result that has both statistical and clinical significance. Worsening encompasses needing to access emergency services, becoming asthmatic, losing the ability to tolerate particular allergens and seeing a reduction in life quality. The deterioration becomes apparent after 5 years and is progressive over 10 years. The risk of developing AR and systemic allergic responses was comparable in both LAR sufferers and healthy controls. Five individuals (3%) developed a systemic allergy more than 10 years after the beginning of the study. Rondón et al. considered that LAR is a clearly distinct disease that rarely progresses to a systemic response, has a natural history of deterioration and carries risk for the development of asthma.

LAR can thus be seen as an independent phenotype of AR in which there are nasal symptoms of AR, in absence of systemic atopy (e.g. positive SPT or raised sIgE titres) are negative. NAC is shown to be positive [1, 22, 35, 36], and allergen-specific immunotherapy can be successful [15, 16]. LAR is thought to represent a subtype of AR, in which the allergic response only affects the nasal mucosa and is a type 2 inflammatory response [4, 37, 38]. Nasal sIgE is present [4, 37, 39–41].

8.5.1 Endotyping LAR: The Role of the Mucosa

Amongst LAR individuals with positive NAC but with the absence of circulating sIgE, detectable levels of nasal sIgE have been found in nasal secretions in 20–40% of the patients [4, 18, 21, 37, 39]. The origin of such sIgE is unknown at present. B cells found in a germinal centre (GC) synthesize immunoglobulins that bind antigen with high avidity. Class switch recombination (CSR) then ensures that the initial IgM isotype is replaced by a different class of immunoglobulin (i.e. IgG or IgA) [42]. Somatic hypermutation affecting the variable portion of immunoglobulins means that isotypes with refined affinity for the epitope are produced [42]. CSR resulting in IgE (termed εCSR) occurs with less efficiency than CSR resulting in the other immunoglobulin subtypes [43]. Indeed, B cells within the GC that are undergoing εCSR have some apparent defect, meaning that apoptosis is at an unusually high level in this group of cells, preventing them from leaving the lymph node.

8.5.2 Phenotyping LAR: Clinical Phenotypes of LAR and Comorbidities

LAR resembles AR in its demographic profile and certain clinical aspects. The archetypal LAR patient is a young, non-smoker female. Rhinitis will usually be from moderate to severe, will be chronic and will be present throughout the year. Comorbid conjunctival inflammation or asthma is frequent. Pruritus within the nose and watery nasal discharge are the usual presenting symptoms, whilst house dust mites are the typical allergen involved [19]. LAR has its highest frequency in young

adults [19], but several studies have demonstrated that it also affects children [19, 44–46] and elderly people [9]. In contrast to individuals suffering from NAR, LAR patients tend to be notably younger and have relatives with atopic disorders, and their symptoms are usually worse [10, 13].

The majority of LAR cases can be linked with a handful of allergenic triggers. Typical triggers are house dust mites (HDM) and pollen from grass or olive trees [4, 22, 35–37, 39, 40]. Mould may also be allergenic [9, 19]. Other less frequently encountered allergens in LAR have not been as extensively studied.

The house dust mite *D. pteronyssinus* is the single most common allergen responsible for causing an allergic response in the nasal mucosa of both patients with AR and LAR. There is an interesting differential pattern of higher sensitization to the mould *Alternaria alternata* in LAR vs AR [9, 10, 19, 35].

Recently, a new phenotype of rhinitis termed dual allergic rhinitis (DAR) has been described in atopic patients. This new phenotype is characterized by the coexistence of LAR to perennial allergens and AR to seasonal allergens in the same individual. These patients suffer from perennial rhinitis but show positive SPT/serum sIgE to seasonal allergens only and positive NAC to both seasonal and perennial allergens associated in both cases with eosinophilic inflammation [47].

8.5.2.1 LAR and Asthma

The frequent association of LAR and asthmatic symptoms led researchers to wonder about the possible existence of an equivalent of local allergic rhinitis at the level of the bronchial mucosa of these patients.

The nature of the bronchial symptoms in LAR has been recently investigated and compared in a study including patients with LAR, AR and NAR with asthmatic symptoms and a group of healthy individuals [48]. Of LAR and AR patients, 28.8% and 83.3% experienced a positive response to the bronchial allergen challenge (BAC), respectively, in contrast to none of the NAR or healthy control subjects [48]. This study also investigated the immunological features of the bronchial inflammation. The allergen exposure induced a significant increase of sputum eosinophils, monocytes and ECP in BAC+ patients regardless of their atopic status, with no changes in BAC individuals [49]. Of note, this infiltrate closely resembles that of airway allergy [7, 50]. Conversely, no sIgE was detectable in the sputum of any of the study subjects [48]. Overall, these data support the existence of a bronchial counterpart of LAR (local allergic asthma) in some non-atopic asthma patients. Moreover, these findings reinforce the united airway concept [2] by demonstrating important pathophysiological links between the upper and the lower airways, also in the case of local allergy.

8.5.2.2 Local Allergic Rhinitis and Conjunctivitis

Ocular symptoms are common in LAR, such as conjunctival pruritus and burning, excessive lacrimation and reddened eyes, both when the allergenic contact has occurred naturally [17] and when provoked by NAPT [2, 13, 19]. Eye-related symptoms are more usual when the allergen involved is a pollen rather than HDM [13, 19]. What is not yet known is whether the conjunctivitis

represents a genuine allergic reaction of the eye proper or is secondary to nasal symptoms and occurs through naso-ocular reflexes [51].

8.6 Treatment

The usual way to manage LAR is to educate patients about LAR, teach them how to avoid the triggering situations and provide symptomatic treatment with antihistamines or nasal steroids, as recommended by the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines [52–54]. Sometimes, unfortunately, it proves unfeasible to avoid the triggers, and therapy that aims to reduce symptoms fails to prevent the development of more severe symptoms and complications [5, 55]. For cases of AR that gain no benefit from drug treatment aiming to reduce symptoms, allergen immunotherapy (AIT) is appropriate. Provided the cases are chosen well, AIT has high levels of efficacy, safety and ongoing benefit after the therapy has been completed [56]. The only therapy that actually modifies the disease process by tackling its cause, and the only therapy that can alter the prognosis, is AIT [49, 52, 54, 57–61].

The pathophysiological similarities between LAR and AR prompted investigators to question whether AIT may have a similar beneficial effect in LAR, as demonstrated for AR [62–65]. Four subcutaneous allergen immunotherapy studies have been published in adult LAR patients to date, demonstrating that AIT is a clinically effective and safe treatment for this condition [62–65].

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Recent Combination Therapy Options for Allergic Rhinitis

9

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9.1 Introduction

The condition in which the nasal mucosa becomes edematous and inflamed is known as rhinitis. Rhinitis can be infectious, noninfectious or a combination of the two [1]. Allergic rhinitis is the most common noninfectious form. Before defining allergy, the concept of atopy should be explained. Atopy is the genetic predisposition to develop IgE against certain substances and is present in some 25–30% of the population. The characteristics of genetic transmission are not fully known, but multiple genes are involved.

Allergy, meaning "to react differently" in Greek, is the presentation of symptoms in sensitive people as a result of overreaction towards certain substances which normally do not cause any reaction. Symptoms such as itching and congestion of the nose, red and watery eyes and sneezing after allergen exposure can be the clinical presentation of allergic rhinitis. Not all atopic individuals will develop allergic diseases. There is a 33% risk of allergy if one parent is allergic and 66% if both are allergic [1, 2]. Allergy development requires that individuals are exposed to the substances (allergens) which can cause the development of symptoms in a context which predisposes to IgE development. Thus, environmental factors acting on a genetic background play a role in the development of allergic rhinitis (AR) [3].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_9

Allergic rhinitis can be classified as seasonal or perennial. However, a more recent classification in the ARIA document uses symptom frequency and severity, and the two do not coincide, i.e. persistent allergy does not equate to perennial rhinitis nor seasonal to intermittent [4]. Persistent allergy includes symptoms lasting more than 4 days a week and more than 4 weeks per year, whereas intermittent allergy is used to describe the condition lasting less than 4 days a week and less than 4 weeks per year. Regarding the severity of the condition when deterioration of daily activities exists, such as not being able to go to school or work, and sleep disturbances are present, the cases can be classified as moderate to severe. If those conditions are not present, the cases are classified as mild allergic rhinitis.

Allergic rhinitis is the most common atopic disease [1]. The prevalence of AR is 20–30% worldwide. AR is detected in 22.7% of the population in Europe and 20.6% in Germany. In Northern European countries, the prevalence is 7%. It seems to be more prevalent in Australia (27.6%). In South America, the prevalence varies between 9% and 21% [1]. In Turkey, studies show that the prevalence of allergy is between 9% and 20% [2, 5–9]. In the United States, allergic rhinitis is the sixth most frequent among chronic disorders [1].

There is some evidence that the prevalence of allergy in urban areas is higher than rural areas (air pollution, lifestyle, better diagnosis and treatment facilities). In addition, AR is more common in those who are educated and with higher socioeconomic status [1].

Allergic rhinitis, though often trivialised, can cause significant clinical, economic and social problems [10–20]. AR results in a small loss (3–4%) of working days in adults and school days in children but frequently results in presenteeism, where attendance happens, but performance is poor, largely due to sleep impairment. If allergic rhinitis is uncontrolled and persists, it may give rise to comorbidities (conjunctivitis, sinusitis, middle ear infections, jaw development disorders, asthma, etc.).

AR therefore deserves considered diagnosis and effective treatment.

9.2 Treatment

9.2.1 Allergen Avoidance

Treatment should be initially preventive through allergen and pollutant avoidance as much as possible. For pollen allergy, it is beneficial to stay away from outdoor activities during the seasons with high pollen density and not to open doors and windows in the morning and evening hours when pollen levels are highest. If the patient has outdoor activities, it is better to remove the clothes upon entering the home, have a shower and wash the hair. Air conditioners should have a pollen filter working by recirculating the room air. Nasal pollen filters and balms can reduce symptoms by about a third [21].

It has been difficult to show that mite avoidance measures are effective in asthma or AR. However, recently, allergen-proof bedcovers reduced asthma

exacerbations in children with severe asthma [22]. It appears that allergen-proof bedcovers plus other measures such as keeping the temperature low and the bedroom well ventilated with low humidity and avoiding soft furnishings should help. Non-allergenic sheets and pillowcases should be used and washed above 60°. In mould allergies, humid surfaces or environments where fungi can grow should be cleaned with bleach or antifungal agents and ventilation improved. The optimal solution in animal allergies is to remove the animal from the indoor environment; failing that, regular washing can be used. Budgerigars and parrots can cause allergies [21].

9.2.2 Medical Treatment

Few patients can be significantly improved by allergen avoidance alone. Most need additional pharmacotherapy. Those with uncontrolled symptoms on this may be candidates for allergen-specific immunotherapy (AIT).

Pharmacotherapy does not change the course of the disease; medications only prevent or reduce symptoms. AIT has been shown to reduce symptoms even after discontinuation, to decrease progression from AR to asthma and to reduce new sensitisations.

Drug categories used in AR medical treatment are as follows:

9.2.2.1 Saline Douching

Meta-analyses [23, 24] show that this is beneficial in both adults and children and is largely free from side effects. It should be widely used in most patients as an initial measure.

9.2.2.2 Antihistamines

They are effective in itching, sneezing and nasal discharge but have little effect on nasal congestion. They bind to H1 receptors, reducing their activity, and are best used regularly to avoid rebound on stopping. A good antihistamine should be effective and fast-acting, without cardiac side effects, long-acting, non-sedative, without anticholinergic side effects, not enhancing the appetite and without any interactions with foods [25].

In addition to oral antihistamines, there are also nasal topical agents such as azelastine [26] and levocabastine, which appear to be more effective on rhinitis. Significant differences favouring azelastine nasal spray were seen for nasal congestion and sneezing in a blinded study versus oral cetirizine. Improvements in overall RQLQ ($P = 0.002$) and individual domain ($P < 0.02$) scores were also larger with azelastine [27].

9.2.2.3 Corticosteroids

In AR, topical nasal corticosteroid sprays (INS) are the gold standard as shown by meta-analyses against oral antihistamines, nasal antihistamines and anti-leukotrienes [28–30]. They are effective in all symptoms, including nasal congestion, and

objectively reduce nasal hyperreactivity [31]. Systemic effects are negligible. They may cause some dryness of the nose, crusting or bleeding; however, these symptoms can be diminished when nasal steroids are used properly, spraying onto the lateral wall and not the septum. Septal perforation is rarely seen in chronic use of INS which actually improves the nasal mucosa and its innate immunity. The effect on nasal obstruction occurs within 7–10 days after initiation [21].

Oral corticosteroids are rarely used because of serious side effects such as hypertension, hyperglycaemia, glaucoma, osteoporosis, etc. Systemic steroids can be used only for a short period of time in selected cases when symptoms are uncontrolled and all other treatments failed [21].

9.2.2.4 Decongestants

They are not used frequently in the treatment of allergies as their role is limited to cases where nasal obstruction is difficult to treat. They can be used systemically or topically helping the management of nasal congestion. They create vasoconstriction in intranasal structures, usually the inferior turbinates releasing the obstruction. Phenylephrine, pseudoephedrine, xylometazoline and oxymetazoline are the most commonly used agents. Their use should not exceed 3–5 days. Systemic decongestant use should be avoided in the elderly, children under 1 year of age, pregnant women, psychiatric patients, glaucoma patients taking beta blockers and patients taking monoamine oxidase inhibitors [21].

9.2.2.5 Cromolyns

They act by mast cell stabilisation. Their role is preventive as they are effective if taken before allergen contact. Their low efficacy and the need for application four times a day make them rarely used; however, their safety means that they are an option in small children and pregnant women [21].

9.2.2.6 Anticholinergics

They are most commonly used in the form of a nasal spray containing ipratropium bromide. They are mainly effective in reducing runny nose, particularly in non-allergic rhinitis. In patients with predominant rhinorrhoea, these nasal sprays provide an effective symptomatic treatment option, either alone or in combination with INS [32]. Side effects include headache and dry mouth [21].

9.2.2.7 Leukotriene Antagonists

Leukotriene receptor antagonists are modestly better than placebo and as effective as antihistamines but less effective than nasal corticosteroids in improving symptoms and quality of life in patients with seasonal allergic rhinitis [29].

They can be part of the treatment plan of AR but not as a monotherapy [21]. They can reduce nasal congestion, rhinorrhoea and ophthalmic symptoms having a beneficial effect in the quality of sleep reducing symptoms during the night. However, even when combined with antihistamine, they are less effective than INS alone [33]. Patients with AR who cannot take intranasal steroids, have sleep disturbances or suffer from asthma are good candidates for leukotriene antagonists [21].

9.2.2.8 Combination Treatments

Some 70% of adult rhinitis sufferers in a tertiary clinic were controlled on INS alone [34]. The remaining 30% need additional treatment. This can be a second drug added in as per guidelines.

The often used combination of oral antihistamine plus INS is in fact no more effective than INS alone [35].

This does not apply if the antihistamine is intranasal. Most of the evidence for this comes from a combined preparation of newly formulated fluticasone propionate and azelastine in a single spray (MP-AzeFlu). Treatment with MP-AzeFlu compared with commercially available FP and azelastine showed a relative difference of 47% to FP and 66% to AZE for nasal symptoms and a relative difference of 58% and 35% to FP and AZE for ocular symptoms in SAR studies. When nasal and ocular symptom scores were combined, MP-AzeFlu was more than twice as effective as either FP or AZE [36]. More patients treated with MP-AzeFlu achieved a halving of their nasal symptom burden (one in every two patients) and complete or near-to-complete response and did so about a week faster than those treated with either FP or AZE [36]. This is relevant in SAR where symptom episodes last 12.5 days [11]. MP-AzeFlu was well tolerated in all four SAR randomised controlled trials [36, 37].

MP-AzeFlu also demonstrated superior efficacy on overall nasal symptoms compared with FP in a 1-year open-label study of patients with chronic rhinitis (i.e. PAR or NAR) [38]. Statistical superiority over FP was noted from day 1 and maintained until week 28, with treatment difference sustained for 52 weeks [38]. In the first month, some 70% of patients treated with MP-AzeFlu experienced complete symptom relief, a median of 9 days faster than those receiving FP. MP-AzeFlu subjects experienced 26 more symptom-free days than FP-treated ones over the year (8.4% more; $P = 0.0005$) [38].

A decongestant and INCS combination (INCS-D) has also been considered for nasal congestion that is not improved by INS. Meta-analysis of six studies did not show benefits of topical decongestants in addition to INCS. Adverse events of INCS-D were comparable with INCS [39].

9.2.2.9 Alternative and Complementary Medicine

The ARIA guideline update states that there is no good evidence for alternative and complementary medicine in AR therapy. This topic is dealt with further in Chap. 13.

9.2.2.10 Allergen-Specific Immunotherapy (AIT)

AIT is an evidence-based effective aetiological treatment for AR. Immunotherapy may be applied when the causative allergens can be detected by patient's history combined with confirmatory skin prick and/or blood tests for allergen-specific IgE. Immunotherapy consists of application of repeated doses of this allergen for some 3–5 years, either regularly or pre-seasonally each year. AIT can be administered experimentally by oral, subcutaneous, sublingual, nasal, bronchial and intralymphatic routes. However, in clinical practice, subcutaneous (SCIT) and sublingual (SLIT) routes are used, with possible slightly greater efficacy in the former but much greater safety in the latter. Because subcutaneous administration of allergens

can occasionally cause severe allergic reactions requiring access to adrenaline and other resuscitative measures, SCIT should be administered in a specialist clinic, whereas SLIT can be self-administered at home after initiation in a clinic [40, 41].

Immunotherapy should not be given to severe immunological patients, patients with autoimmune diseases, psychiatric patients, patients with malignant diseases, patients with severe or uncontrolled asthma, those taking beta blockers, those with severe cardiovascular disease and children below the age of 5. If a female patient becomes pregnant during immunotherapy, the treatment is continued without problems. However, patients cannot start immunotherapy during pregnancy [21].

9.3 Surgical Treatment

There is no surgical treatment of AR as monotherapy. However, when a concomitant septal deviation with allergic rhinitis makes difficult the local application of drugs or enlarged inferior turbinates are not responding to nasal sprays and block the nose, then surgery may be a treatment option. Especially in traumatic septal deviations when the nasal patency is severely blocked, then maybe it is better to proceed primarily in a surgical correction of the septum in order to create optimal conditions for local application of drugs.

Enlarged inferior turbinates are a common result of long hıstory of AR requiring some kind of cauterisation or tissue reduction. When turbinates respond to vasoconstriction radiofrequency, cauterisation is the preferable option. In cases of fibrotic turbinates or with polypoid changes, turbinoplasty or tissue reduction with shaver is recommended taking care to preserve the mucosa as much as possible and to avoid aggressive surgery.

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Does Allergy Cause Chronic Rhinosinusitis with Nasal Polyps?

10

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10.1 Introduction

Chronic rhinosinusitis (CRS) is a multifactorial disease due to chronic inflammation of sino-nasal mucosa that persists for more than 12 weeks. Since the first edition of EPOS guidelines, CRS has been divided into two main phenotypes: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP). In recent years, several authors agreed that CRS is not a uniform disease process but rather includes different phenotypes and endotypes. Differences may be observed in terms of risk factors, co-morbid conditions associated with CRS and disease control by medical treatment and surgery [1]. Unfortunately, over the years, CRS has been ill-defined and viewed in different ways by specialists in different fields. Nowadays, however, groups of experts have convened to deliver consensus on the definition, assessment and management of CRS, and in particular the recent EPOS2020 guidelines [2] represent an important step forward [3], providing revised, up-to-date and clear evidence-based recommendations and integrated care pathways in CRS.

CRS associated with nasal polyp formation (CRSwNP) characteristically features nasal polyps within the middle meatus and present on both sides. Nasal polyps are translucent, between yellow and grey or white in colour, have a glistening appearance and contain inflammatory exudate with a gelatinous consistency. They are found in the lining of the nose or paranasal sinuses. Since polyps have a poor blood supply, they tend to be greyish white in appearance. Despite the increasing

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_10

knowledge regarding pathophysiology of CRS, the aetiology is still discussed. Several factors may contribute to the development of CRS such as epithelial barrier dysfunction, defects in innate immunity, alterations in microbiome composition, biofilm, congenital factors, etc., promoting inflammation with different cellular and biochemical pathways [2].

The role of allergy in chronic rhinosinusitis (CRS) has been largely discussed in the literature, but nevertheless it remains controversial. Allergy and CRS are very prevalent diseases and frequently co-occur; however, direct causality has never been clearly demonstrated. Because the association between the two diseases has not been clear for years, making an evidence-based decision of whether to evaluate or treat allergies in CRS patients was difficult. Recently, it is clear that the prevalence of allergy is variable between the different subtypes of CRSwNP and the association seems to be very strong particularly with allergic fungal rhinosinusitis (AFRS) and central compartment atopic disease (CCAD) [1–3].

10.2 Epidemiologic Data Demonstrating Link Between Allergy and Chronic Rhinosinusitis with Nasal Polyps

The majority of studies support the notion that the association between polyposis and non-allergic disorders is stronger than that between polyposis and allergic conditions. Nasal polyposis is more frequent in cases of non-allergic asthma (13%) than in allergy-associated asthma (5%). Several studies demonstrated that nasal eosinophilia is an important risk factor for development of nasal polyps, and it is more often associated with a non-allergic status. De Corso et al. [4, 5] demonstrated that non-allergic eosinophilic patients had a high risk of NP development over the years; the authors suggested that early detection of nasal eosinophilic inflammation in non-allergic patients represents an early marker for identification of a more aggressive inflammatory phenotype of nasal polyps. Accordingly, Chen et al. [6] demonstrated that nasal eosinophilia is a significant factor related to the morbidity of CRSwNP in Northwest China. Elevated eosinophil levels occurring in the context of non-allergic rhinitis patients constitute a risk factor for the development of nasal polyps in chronic rhinosinusitis patients. Similarly, elevated eosinophil levels occurring in the context of allergen-negative rhinitis are also an important risk factor for morbidity of CRSwNP.

The relationship between allergy and chronic rhinosinusitis (CRS) has been largely discussed, and it has been controversial over the years [7]. In particular, studies aiming to demonstrate the role of allergy in the two major phenotypes CRSwNP and CRSsNP have been often inconclusive and controversial, with a poor level of evidence. Wilson et al. [8] in 2014 published an evidence-based review on the association between allergy and chronic rhinosinusitis with and without nasal polyps. The authors analysed a total of 24 articles meeting the inclusion criteria. They demonstrated that the number of articles demonstrating an association between allergy and CRSwNP was not significant different since articles showing no association. The same contradictory evidence was observed for

articles that examined the relationship between allergy and CRSsNP. The authors did not find articles examining outcomes of CRSsNP or CRSwNP following allergy treatment. The authors concluded that based on the analysed data, the recommendation was that allergy testing and treatment were an option in CRSwNP and CRSsNP patients.

Since 2014, a few significant studies have been published on the topic. In the literature over the years, there has been large heterogeneity in the definitions of allergy and CRS; for this reason, it has been difficult to establish the manner and degree by which allergy contributes to CRS. Recently, a clear definition of different phenotypes and endotypes of CRS has been pointed out. In particular, recently, authors from the UK [9] underlined that a variable association between allergy and different subtypes of CRS exists. The analysis included 1470 study participants: 221 controls, 553 CRSsNPs, 651 CRSwNPs and 45 AFRS. The prevalence of inhalant allergy was 13.1%, 20.3%, 31.0% and 33.3%, respectively; house dust mite allergy was significantly higher in CRSwNPs (16%) compared to CRSsNPs (9%) in this study. More interestingly, Marcus et al. [10] focused the attention on the association between allergy and two distinct phenotypes of CRSwNP: allergic fungal rhinosinusitis (AFRS) and central compartment atopic disease (CCAD). In conclusion, the prevalence of allergy in CRS may vary largely by phenotype, with CCAD and AFRS having a stronger association than CRSwNP and CRSsNP.

10.3 Pathophysiology of the Association Between Allergy and Chronic Rhinosinusitis with Nasal Polyps

There are a number of questions that need to be answered with reference to the complicated immune pathophysiology of CRS and concerning the role of IgE, mast cells and eosinophils. To what extent is inflammation a pure allergic response? To what extent do persistent attack by microbes and a subsequent breakdown of immune tolerance in a confined region contribute to the synthesis of IgE and mast cell and eosinophil activation? How much of the activity of mast cells and eosinophils occurs without IgE acting as intermediary? Being able to answer such queries will assist in subtyping CRS and finding suitable management strategies [9].

For years, the evidence has been unclear whether IgE-type allergic responses are more prevalent in individuals with CRS than healthy individuals. An allergic response through IgE is readily demonstrable in some patients, by observing a raise in total and specific serum IgE (sIgE) and noting positivity of skin prick testing; nevertheless, it has not been possible to demonstrate that allergic responses are a significant cause of the inflammatory response in the nose and sinuses in CRS patients. For several authors, it could be more properly due to a sensitisation process as a consequence of epithelial barrier failure. Nonetheless, even non-atopic patients may have mucosae with significant amounts of IgE, eosinophilic infiltration, mast cells and Th2-associated cytokines. Elevated numbers of Th2 (T helper type 2) cell-associated cytokines and interleukins 5 and 13, plus raised histamine levels, are

usually found within non-allergic polyps. In a subgroup of cases of both CRSwNP and CRSsNP, the mucosa contains high levels of sIgE, cells with receptors for IgE, eosinophils and mast cells [11, 12].

In addition to the increase in cytokines and chemokines described above, several other molecules are also present at higher levels in nasal polypoid biopsies: histamine, albumin, sCD23 and IgE. In tissue and fluids derived from polyps, the level of the isotypes IgA, sIgA, IgE, IgG and IgM is also elevated. But the level of sIgE is only increased where an allergy to an aeroallergen exists. IgE levels and EG2+ cellular numbers are highly correlated. In polyps from patients with aspirin-intolerant asthma, more peptido-leukotrienes are released than normal, and there is a corresponding decrease in the level of secreted PGE2 from both the polyp itself and circulating blood cells. Plasma cell levels are often raised in the mucosa from CRS patients, the highest amounts being found in CRSwNP, compared to healthy mucosa. A certain number of individuals with CRS also have high serological and mucosal levels of sIgE and the isotypes IgG and IgA. This elevation occurs, whether the subject has atopy or not [13, 14].

Nasal polyps may also contain high levels of sIgE against superantigens found on bacteria, and this may direct the involvement of eosinophils in the inflammatory response and particularly in the more severe phenotype as a maladaptive local response of the immune system. The localised synthesis of sIgE to staphylococcal enterotoxins indicates a locally occurring hypersensitivity reaction to the presence of colonisation by *S. aureus*. Staphylococcal enterotoxins are superantigens, with the ability to cause widespread T cell activation. Despite serological titres of sIgE to enterotoxins being below the detection range, assays for sIgE on sinusal mucosa are elevated in cases of CRSwNP. In cases of CRSsNP, such sIgE to enterotoxins are not synthesised [15–18].

It has been proposed that fungi may act to prime the Th2 and eosinophilic response seen in some subtype of CRSwNP such as AFRS in which a high level of sensitisation to *Candida* or *Alternaria* organisms may be observed [19–22].

The combined IgE and sIgE levels to bacterially derived enterotoxins and epitopes on fungi may both be higher in CRSwNP than in CRSsNP or in healthy people. The high levels of IgE within the mucosa of such cases may be a physiological response to the presence of the colonising bacteria associated with CRSwNP or the fungi frequently seen in eosinophil-containing mucus produced in AFS. A competing explanation for these findings is that superantigens derived from bacteria or fungi lead to derangement of IgE-associated mechanisms in patients with a genetic predisposition who have developed hypersensitivity. In certain cases of CRSwNP, there are raised levels of sIgE to staphylococcal superantigens, and the levels may correspond to how severe the disease becomes. Superantigens may react with receptors on B and T lymphocytes or the major histocompatibility complex and cause IgE to be manufactured. Superantigen therefore acts directly on B lymphocytes and indirectly through altering T lymphocytic behaviour to initiate class switching and the synthesis of sIgE. In this context, allergy, superantigens and fungi are considered disease amplifiers because they may increase the inflammatory process associated with nasal polyp development [15, 23–27].

10.4 Subtypes of CRS in Which a Link Between Allergic Rhinitis and Chronic Rhinosinusitis Has Been Demonstrated

10.4.1 Allergic Fungal Rhinosinusitis

It was originally described by Safirstein [28] and Katzenstein et al. [29]; over the years, several authors have questioned whether the condition really exists as a separate clinical entity or is part of eosinophilic CRS or CRSwNP. Recently, the EPOS guideline has pointed out that allergic fungal rhinosinusitis (AFRS) is a subset of polypoid chronic rhinosinusitis that is characterised by the presence of eosinophilic mucin with noninvasive fungal hyphae within the sinuses and a type I hypersensitivity to fungi.

AFRS accounts for about 0–8.2% of CRS cases with variation according to geographical distribution. AFRS is most prevalent in warmer wetter climates such as the Mississippi basin and western India, where Bombay has a rate of 8.2%. AFRS is more prevalent in younger people, those with poor socioeconomic status and females. Atopy is a pathognomonic feature of patients with AFRS, and concomitant allergic diseases, such as allergic rhinitis and childhood-onset asthma, are common in this group. The defining pathophysiology in AFRS is sensitisation to the causative fungus as a primary and requisite feature along with mucin colonised with noninvasive fungus. Although fungal sensitisation may exist in CRSwNP, typically IgE levels are higher in AFRS.

The major criteria [30] consist of the following:

1. Diffuse or localised nasal polyps
2. Fungi on staining
3. Eosinophilic mucin without fungal invasion into sino-nasal tissue
4. Type I hypersensitivity to fungi
5. Characteristic radiological findings with soft tissue differential densities on CT scanning and unilaterality or anatomically discrete sinus involvement

The minor criteria [31] include bone erosion, Charcot-Leyden crystals, unilateral disease, peripheral eosinophilia and positive fungal culture along with:

1. The demonstration of the characteristic eosinophil-rich allergic mucin visually or histopathologically
2. A positive fungal stain or culture from the sinus at surgery
3. The absence of immunodeficiency or diabetes

10.4.2 Central Compartment Atopic Disease (CCAD)

Central compartment atopic disease (CCAD) is a recently described variant of chronic rhinosinusitis with nasal polyp (CRSwNP) associated with inhalant allergy.

Evidence of the literature recently confirmed that CCAD represents a clinically distinct phenotype of CRSwNP with a high prevalence of allergy and low prevalence of asthma [32].

Several studies supported the association between oedematous/polypoid changes of the middle turbinate (MT) and positive allergy [33].

CCAD, described for the first time in 2017, is a nasal inflammatory polypoid condition strongly associated with inhalant allergy, involving the superior nasal septum (NS) with or without the MT and/or superior turbinate (ST); it primarily involves the central compartment nasal mucosa, with the sinuses becoming involved by obstruction in advanced disease. Inhalant allergen deposition in these central compartment structures is related to the course of normal nasal airflow. In clinical practice, a low association of CCAD with asthma was also noted [34, 35].

10.5 Management of Allergy in CRS Patients

A large proportion of CRS have been sensitised to a particular allergen. It is more usual for sensitivity to year-round allergens, such as house dust mite (HDM), cockroaches, animal dander and fungi, to have occurred than for allergy to pollen to be present. Allergy may have an important role in some patients as disease amplifier and in some subtype as aetiological factor. Therefore, it seems reasonable to assess allergic sensitivity in all CRS patients, particularly to the year-round allergens and fungi. There is a benefit in identifying an allergic sensitivity to specific allergens such as HDM, as it allows a strategy of avoidance to be advocated, which may improve symptoms [36, 37].

Despite a strong recommendation for allergen immunotherapy (IT) in patients with allergic rhinitis (AR), its role in CRS remains less certain; research investigating possible benefit of immunotherapy in CRS are few and of poor quality. De Young et al. [36] in a systemic review looked at sinusitis-specific outcomes in CRS patients who underwent IT. They demonstrated symptom reduction in the short term; however, they included seven studies in which quality led to weak conclusion. Equally, studies that examined the role of IT in the treatment of AFRS have a relatively low level of evidence. Current CRS treatment recommendations specify allergy testing and treatment as an option [38].

Considering that pathophysiology of CRSwNP is characterised by prominent local production of IgE that may contribute to chronic inflammation by continuously activating mast cells, it would be logical that anti-IgE would be efficacious in its treatment. One early study demonstrated lower symptom scores (change from baseline in anti-IgE group) and a significant reduction of NPS on endoscopic examination and of Lund-MacKay scores on radiologic imaging [39]. Recently, the phase III POLYP 1 and POLYP 2 trials showed omalizumab met both co-primary and multiple secondary endpoints in adults with CRSwNP poorly controlled on intranasal corticosteroids. The co-primary endpoints at 24 weeks were change from baseline in nasal polyp score (NPS) and change from baseline in average daily nasal

congestion score (NCS). Key secondary endpoints that were met included improvement in the sino-nasal outcome test-22 (SNOT-22) health-related quality of life assessment, sense of smell, postnasal drip (posterior rhinorrhoea) and runny nose (anterior rhinorrhoea). The safety profile in these trials was consistent with the known safety profile for omalizumab. Currently, the FDA is considering a supplemental licence application for the use of omalizumab in nasal polyposis.

10.5.1 Recent Advances in Immunology

The paradox of eosinophilic inflammation without evidence of IgE may be explained by recent advances in immunological knowledge which has led to the redesignation of eosinophilic asthma from Th2 to T2 asthma. This is because there are two lineages of T cell: the long-known adaptive ones (including Th2) that reside mainly in lymphoid tissues and the recently identified innate ones (ILCs) that reside in peripheral tissues and are particularly abundant at barrier surfaces where they respond rapidly to tissue perturbation, producing cytokines within hours of being activated, in contrast to the days required for naive adaptive lymphocytes to be primed, expand, differentiate and enter tissues.

ILCs lack antigen-specific receptors and do not undergo genomic receptor rearrangements or clonal selection unlike T and B cells. Their reaction to challenges to their local tissue is specified during their development, not at the time of immune assault. However, ILCs exhibit functional diversity which mirrors that of T cells: three major subsets ILC1, ILC2 and ILC3 [40] corresponding to Th1, Th2 and Th17 helper T cell subsets have been identified. Roles in inflammation and in response to intracellular pathogens, helminths and extracellular bacteria or yeast exist [41, 42], similar to those of their T cell analogues.

ILC2s, activated by alarmins such as TSLP, IL25 and IL-33 triggered by environmental factors such as viruses, pollution and antigens, are probably relevant to the pathogenesis of CRSwNP. Poposki et al. [43] reported that all ILCs are present in nasal polyps, with ILC2s predominant and significantly elevated compared to levels in CRSsNP and normal sinus tissue. They may represent early events in polyp development [44] and may play a role in the activation and survival of eosinophils [45]. The ILC2s also promote the proliferation of Th2 cells [46]. In CRSwNP, synergy occurs between ILC2s, eosinophils and Th2 cells. ILC2s activate the eosinophils and prolong their survival; pre-activated eosinophils can enhance IL-5 production of ILC2s in an IL-4-dependent manner [47]. In CRSwNP, systemic corticosteroid treatment can reduce ILC2s and increase ILC2 apoptosis [44, 48]. Padro Dietz et al. [49] reported equivalent levels of ILC2s and a small trend towards increased Th2 cell numbers in AFRS. AFRS may result from defects in the innate immune system reflected by the inability to clear fungi from the sinuses.

It is likely that ILC2s play important roles in CRSwNPs and represent novel therapeutic targets.

10.6 Conclusion

The role of allergy in the pathogenesis of chronic rhinosinusitis with nasal polyps has been discussed for years. Nowadays, it has been clarified that allergy can be considered a disease amplifier in some cases of CRSwNP; otherwise, a stronger association with allergy has been observed with particular subtype of CRSwNP such as CCPD and AFRS. In both cases, an accurate diagnosis and adequate allergy management must be taken into consideration.

Recent advances in immunology have revealed new lymphocyte subsets called ILC2s are implicated in upper respiratory tract inflammatory disease as well as in asthma and could represent important new targets for treatment.

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Is Allergen-Specific Immunotherapy (AIT) Helpful in Treating CRSwNP?

11

Meltem Tendoğan Avcı, Cemal Cingi, and William Reisacher

11.1 Introduction

Chronic rhinosinusitis is a set of conditions involving inflammation, but its precise pathogenesis is, at present, unknown. CRS exhibits phenotypical heterogeneity, which is divided into two types: with nasal polyps (CRSwNP) and without (CRSsNP) nasal polyps. CRSwNP has been closely associated with allergic rhinitis (AR) due to the co-occurrence of the two and because both involve inflammation. The relationship between AR and CRSwNP remains subject to considerable debate, with the data gathered so far not pointing clearly in one direction. CRSwNP is being seen as a disorder wherein inflammation plays a key role and both the innate and adaptive immune systems are involved. Reports currently emerging have sought to explain the apparent paradox of cases where a patient has no systemic allergic response, yet does benefit from anti-IgE treatment, as representing a localized IgE-mediated allergic response [1, 2].

The benefit in managing CRSwNP using the same pharmacological approach as taken in AR, particularly in CRSwNP cases with co-morbid AR, has been reported elsewhere [3].

There is frequent overlap between the symptoms of patients with AR and CRSwNP. It is advised that any CRS patient in whom pharmacological therapy has failed to control symptoms also be investigated for allergy and treated accordingly. If a patient with CRSwNP plus AR has no relief from symptoms in spite of

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_11

environmental adaptations alongside pharmacological therapy or if symptoms are present for more than half the year, allergen-specific immunotherapy (AIT) should be considered if one or two allergens can be shown to be driving the disease. Individuals with a history suggesting food allergy or intolerance should also undergo food allergy testing and be offered dietary advice on how best to avoid the offending food [1].

11.2 Nasal Polyposis and Allergy

CRSwNP is classically associated with eosinophilic inflammation typified by T cells, IgE, histamine, eosinophilic cationic protein (ECP) and inflammatory cytokines such as IL-5 and IL-13 [4]. Mast cell degranulation is seen in nasal polyps. Drake-Lee studied 36 polyps to see if histamine was released when they were challenged with anti-IgE and allergens. Eight patients released histamine from polyp tissue but only three with both anti-IgE and allergen extracts. He concluded that although allergy may cause mast cell degranulation in polyp tissue, it is unlikely to be a common cause of nasal polyps [5]. Other investigators think that allergies could be a factor in nasal polyp formation, alongside the presence of fungi or bacteria. They cite three pieces of evidence that point to a role for allergy in aiding nasal polyp formation: most polyps contain high levels of eosinophils, asthma often co-occurs and nasal symptoms and signs overlap with those of an allergy [6].

These can be refuted since eosinophil ingress is now known to occur by non-allergic mechanisms (see Chap. 10); asthma is not necessarily allergic, particularly in adults (hence T2 asthma, rather than Th2); and nasal symptoms are necessarily restricted in repertoire. Itching and sneezing are much more common in AR than in CRSwNPs. Although mucosal IgE is implicated in the pathophysiology of some CRSwNP, the mechanisms for IgE synthesis appear to be non-allergic and related to bacteria, particularly *Staphylococcus aureus*. The varied phenotypes and endotypes seen in CRSwNP involve dysfunction of the epithelial barrier, a T-helper cell environment, altered eicosanoid metabolism, delayed healing and interactions with bacteria leading to disease exacerbation [7].

Higher levels of positivity to skin prick testing (SPT) in individuals with polyposis than in the general population. A separate research project found that individuals in whom SPT was positive were at greater risk of previous nasal polyp removal on several occasions [8]. There remains a discussion about the status of any relationship between atopic disorders (i.e. inherited predisposition to hypersensitivity to particular allergens, namely, pollen, house dust mite, mould and animal dander) and polyp formation in the nose [9].

11.2.1 Aspirin Hypersensitivity

Multiple studies have characterized aspirin intolerance as a distinct disorder known to be associated with the formation of nasal polyps. Aspirin hypersensitivity is

defined as a "distinct clinical syndrome, characterized by the precipitation of rhinitis and asthma attacks by aspirin and most of the other non-steroidal anti-inflammatory drugs (NSAIDS)" and is now called NSAID-exacerbated respiratory disease (N-ERD) [10]. The use of aspirin desensitization in the treatment of N-ERD is considered in Chap. 12.

11.3 Treatment of Allergies with Immunotherapy

Immunotherapy for specific antigens activates regulatory T cells, among other events. The mechanisms by which this occurs have become better understood recently. Radulovic et al. [11] noted that successfully implementing subcutaneous immunotherapy (SCIT) for antigens in timothy grass over 2 years led to an increase in the level of Foxp3-positive CD41CD251 (TR1 cells) found in the nasal mucosa from patients with seasonal AR. Furthermore, SCIT promoted a second rise in the number of TR1 cells during the season when pollen appears and a fall in eosinophils and cells that release interleukin 5. In a research by Francis et al. [12], SCIT for the timothy grass cluster antigens was given for 2 months, and then 20 mg of Phl p 5 was administered for the following 10 months as maintenance. Initially, there was a rise in interleukin 10 production by PBMCs when the individual was exposed to the grass allergens. Thereafter, basophil histamine release markedly decreased when challenged with grass allergens at the 6-week mark. Specific IgE to grass rose (isotypes IgG4 and IgA), but there was inhibition of the reaction to grass allergens when week 12 was reached. It is possible that the rise in IL-10 levels occurring early on may be the event precipitating the formation of IgG4 and IgA.

Yamanaka et al. [13] observed that sublingual immunotherapy for Japanese cedar pollen (Cry j 1 and Cry j 2) led to the formation of Treg 1 cells with specificity for cedar, but a clonal expansion of Treg 1 cells was not apparent when examined by looking at receptor expression on T cells. Furthermore, TR1 cells prevented T cells from proliferating in response to a broad range of stimuli (CD3/CD28 antibodies). This finding may indicate that TR1 cells activated by contact with an allergen may prevent Th2 cells responding to allergens other than those found in the immunotherapy preparation. Allam et al. [14] biopsied oral mucosa, which they then studied ex vivo. When the timothy grass-derived allergen Phl p 5 was presented, Langerhans cells became less capable of maturing but did migrate further, as well as secreting raised levels of TGF-b1 and interleukin 10. These last two molecules are important for Treg cells to differentiate. Viewed as a whole, all these studies help to illuminate aspects of how Treg cells are produced and function during the course of specific immunotherapy [15].

Immunotherapy is available in the form of a subcutaneous injection (i.e. SCIT) or sublingual delivery (i.e. SLIT). SCIT exerts its effects by reducing Th2 activity in response to allergen presentation, leading to lowered levels of interleukins 4, 13, 5 and 9. The declining activity of the Th2 pathway leads to greater dominance by a Th1 coordinated response to allergenic stimulation. Immune tolerance appears to occur through Treg release of interleukin 10 and TGB-beta, which seemingly

prevent the Th2 pathway involvement. SCIT leads to a number of results that produce benefit, as shown by the way serum taken from individuals post-SCIT inhibits binding of IgE complexed to antigen to B lymphocytes in vitro and the inhibition of responses by allergen-specific T cells when presented with IgE complexed to antigens [16].

The main difference between SCIT and SLIT is that, in the latter, therapy is administered via the mouth, contacting the oral cavity mucosa. The changes induced by SLIT mirror those brought about by SCIT, namely, downgrading of Treg cells via raised IL-10 early on in treatment, together with the blocking of specific responses to the antigen and alterations in the activity of T lymphocytes with specificity for the allergen as immunotherapy comes to an end. One difference is that SLIT does not stimulate TGF-beta release (unlike SCIT) and thus SLIT may be less potent in its capability of producing Tregs with specificity for the allergen [16]. However, local mucosal changes in salivary IgA shown in SLIT may confer additional benefit [17].

To summarize, AIT, both SCIT and SLIT, downregulates the inflammatory responses to triggering allergens.

11.4 Nasal Polyps and Immunotherapy

In a local study of 90 Kentucky polyp patients, many of whom were allergic, Yun showed that immunotherapy treatment had no statistically significant effect on the number of revision surgeries or on the time to the recurrence of nasal polyps. Asthma and aspirin hypersensitivity correlated with higher CT scores or more severe disease. The presence of eosinophils in polyp tissue did not affect the CT score. Those with a higher CT score showed a shorter time to polyp recurrence [18].

El-Samny et al. looked at how immunotherapy affected the chances of nasal polyps reforming in atopic individuals following surgical removal of the polyp [19]. Compared with those who had AIT alone, those who underwent both surgery and postsurgical AIT reported greater satisfaction, but the difference was not statistically significant: 38.9% of the surgery plus immunotherapy group (group 1) had regrowth of nasal polyps, compared with 30% in the immunotherapy only group (group 2). The individuals in group 2 had a lower nasal polyposis score, but the score remained raised. Recurrent nasal polyps formed in the period 7–13 months in group 1 and in the period 12–16 months in group 2. The study authors' conclusion was that immunotherapy in allergic patients who suffer from nasal polyps is suitable for implementation following surgery to reduce the size of polyps and to give a better quality of life and less troublesome symptoms. They cautioned that immunotherapy alone would not offer adequate benefit in every case of nasal polyposis. El-Samny et al. [19] also proposed that the rate of regrowth of nasal polyps may slow if SCIT is prolonged.

Nishioka et al. reported on polyp recurrence rates in patients with CRSwNP and perennial allergies who started immunotherapy around the same time they received endoscopic sinus surgery (ESS), compared to similar patients who declined immunotherapy [20]. With a mean follow-up of 14.9 months, 12/34 (35.3%) of patients

receiving immunotherapy experienced a recurrence in polyp disease in 13/58 (22.4%) operative sides, while 2/5 (40%) of the non-immunotherapy patients experienced a recurrence in 4/8 (50%) operative sides. The small size of the control group precluded statistical analysis.

11.5 Conclusion

According to what is currently known and recommended by guidelines, allergy assessment in cases of CRSwNP is discretionary [21]. It is uncertain whether AIT is beneficial in CRSwNP, given the absence of good-quality RCTs. The lack of supportive evidence, and the heterogeneous nature of the disease and of data currently available, means that it is not possible to make a recommendation to use immunotherapy in CRSwNP [1]. However, in subjects with CRSwNP plus AR uncontrolled by pharmacotherapy, AIT should be considered.

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Does Aspirin Desensitisation Work in N-ERD?

12

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12.1 Introduction

Aspirin (ASA, acetylsalicylic acid) has the most widespread use of any medication in the world. It plays a key role in the management of cardiovascular disease, especially acute coronary syndromes (ACS) and chronic ischaemic heart disease (CIHD). It is used to prevent stroke and in the management of certain chronic rheumatological disorders. Unfortunately, however, patients may become hypersensitive to aspirin or other agents of NSAID (nonsteroidal anti-inflammatory drug) type. This is particularly so when the agent is predominantly an inhibitor of the cyclo-oxygenase 1 (COX-1) enzyme [1].

Nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD), also referred to as Samter's triad, affects both the upper and lower airways and involves sinusitis of eosinophilic type, severe nasal polyp formation, asthma and hypersensitivity to COX-1-inhibiting drugs. It is an inflammatory disease of escalating severity. Of N-ERD sufferers, 75% are also sensitive to alcohol [2]. N-ERD has a frequency of between 0.6% and 2.5% in general and is seen in 40% of cases where the patient develops asthma in adulthood and has chronic sinusitis with nasal polyposis (CRS(+)NP). N-ERD is found in 7% of those with asthma, with a peak occurrence rate of 15% if asthma is severe [3]. The disorder is classified as progressive. The most common age for it to occur is age 30–34, and it is more usual in females than males. The initial presentation of N-ERD is frequently a

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_12

flu-like illness that develops into persistent rhinosinusitis; then, asthma signs develop and finally frank respiratory system sensitivity to aspirin and NSAIDs [4, 5].

The use of ASA for secondary prevention in cases of coronary arterial disease (CAD) is virtually universal. ASA has been employed both in NSTEMI (probable or certain myocardial infarction without elevation of the ST segment) and STEMI (myocardial infarction with ST elevation) and has diminished re-infarction rates and saved lives [6]. Sadly, the use of ASA in CAD may be limited, despite its potential to reduce mortality, where there are concerns about a patient's previous hypersensitive responses to aspirin. There are fairly frequent reports of individuals experiencing hypersensitivity after receiving ASA for CAD, with one study, which involved 9565 such individuals, reporting an occurrence rate of 1.5% [7]. Thus, for a patient with CAD and ASA hypersensitivity, challenge with ASA to induce desensitisation ought to occur commonly. Despite this rationale, the study quoted [7] found that ASA was deliberately not given in 76.1% of cases, with only four individuals actually being given ASA desensitisation procedures [1].

12.2 Pathogenesis of N-ERD

Whilst the precise pathogenetic mechanism of N-ERD remains only partially known, it is thought that aberrant biochemical pathways involving arachidonic acid are important. This biochemical disturbance leads to raised leukotriene LTE4, and resting levels of prostaglandin PGE2, which inhibits inflammation, are diminished [8]. Histopathological changes include massive eosinophilic infiltration, with abundant mast cells and thrombocyte-leucocyte aggregation. In circulating granulocytic cells, leukotriene C4 synthase produces LTC4, more than 50% of which is produced in thrombocyte-granulocyte aggregates. The increase in aggregate numbers in N-ERD therefore signifies a rise in LTC4 [9]. A key role for interferon-γ (IFN-γ) in the pathogenesis of N-ERD was shown by Steinke et al. [10]. It was discovered that IFN-γ was the dominant cytokine in samples taken from N-ERD sufferers, followed by interleukin-4 (IL-4). IFN-γ had a powerful effect on eosinophilic degranulation, as well as promoting transcription of genes that partake in the production of cysteinyl leukotrienes. N-ERD seems to involve derangement of both the T1 and T2-mediated immune pathways. In this respect, it differs from CHES (chronic hyperplastic eosinophilic sinusitis), which mainly affects the T2 pathway [10].

How this pathogenetic mechanism is altered by aspirin desensitisation is not yet understood. Some initial findings include diminished expression of the cysLT1 receptor, prevention of LTB4 synthesis, lower levels of IL-4 in sputum and reduced secretion of LTE4 [11–13]. Overall, as reflected by the levels of different mediators, the metabolism switches from a proinflammatory to an anti-inflammatory state [14].

N-ERD thus depends on complicated metabolic derangements occurring within the arachidonic acid pathways, at least some of which depend on an inherited predisposition [15, 16]. There is excessive synthesis of the proinflammatory eicosanoids that promote bronchoconstriction, in particular, LTC4 and PGD2. Simultaneously, there is underproduction of anti-inflammatory signalling molecules, notably

prostaglandin E2. The subtype of asthma that exhibits sensitivity to ASA therefore involves massive inflammatory cell infiltration by eosinophils, a response involving extensive T2 lymphocytes and degranulation of mast cells [15–17].

12.3 Aspirin Desensitisation

12.3.1 Indications for Aspirin Challenge

Aspirin challenge is needed to make a formal diagnosis of N-ERD in subjects without a history of a reaction to aspirin and to another NSAID.

12.3.1.1 Aspirin Desensitisation

This can be used as a therapeutic measure in N-ERD; it also protects against inadvertent ingestion of an NSAID and allows for therapy with NSAIDs for analgesia, cardiovascular disorders, etc. [18–21].

Two methods are used: oral and intranasal.

12.3.2 Aspirin Desensitisation and Aspirin Therapy

Prior to undergoing oral ASA challenge and AD, candidates for the treatment in whom N-ERD is the putative diagnosis are given leukotriene antagonists, the purpose of which is twofold: to provide therapy for N-ERD itself and to attenuate the response in the lung when ASA is presented, without preventing the naso-ocular reflex from functioning [22–25]. Nasal corticosteroids are stopped 1 week prior to challenge; long-acting beta-agonists and inhaled steroids are not stopped. No oral corticosteroid should be given in the month before challenge. The ideal time frame for undertaking AD is 2–4 weeks post-sinus surgery aiming at reducing the bulk of intranasal polyps, since continuous ASA treatment hinders polyps from reforming. It is suggested that FEV1 before bronchodilator use be at least 70% of the best result obtained from that individual and at least 1.5 L in volume [18]. AD is contraindicated if the patient is pregnant, asthma is brittle or gastric ulceration or bleeding disorder is present. The patient should provide informed consent to the procedure [26].

12.3.2.1 Oral Aspirin Challenge

Oral challenges have to be carried out under the direct supervision of a physician and technicians skilled in performing provocation tests with aspirin. Emergency resuscitative equipment should be readily available. Patients should have an intravenous line attached. The patients should be in a stable clinical condition. Baseline FEV1 should be at least 70% of the predicted value for oral challenges with aspirin [27].

If regular treatment with oral corticosteroids is required, the dose should not exceed 10 mg of prednisolone or equivalent. The dose of inhaled (bronchial) and

local (nasal) corticosteroids should be as low as possible and should be kept stable throughout the duration of the challenge. Any therapy with corticosteroids should be carefully recorded, as they may blunt any response to aspirin [28].

Challenge protocol—day 1 (placebo). Forced expiratory volume in 1 s is measured, and the baseline value is chosen as the best of three efforts (which do not differ by more than 10%). The challenge is started if the baseline FEV1 is at least 70% of the predicted value for the patient. Three (or optionally four) capsules of placebo are administered at 1.5–2-h intervals. Forced expiratory volume in 1 s is measured every 30 min, and the values are allowed to vary by <15% from baseline. If a greater variation in FEV1 occurs, the patient is deemed in an unstable clinical condition and therefore is excluded from any further challenge [27].

Challenge protocol—day 2 (aspirin). Forced expiratory volume in 1 s is measured, and the baseline value is chosen as the best one of three consecutive efforts. The challenge commences when the baseline FEV1 is at least 70% of the predicted value. Usually four exponentially increasing doses of aspirin (27, 44, 117, 312 mg) are administered every 1.5–2 h until a cumulative dose of 500 mg is reached [27].

If a patient has a history of a severe reaction (very severe dyspnoea and/or anaphylactic shock) after aspirin or other NSAIDs, the test is commenced with 10 mg of aspirin, and the next dose of 17 mg is administered 1.5–2 h later, i.e. the 27 mg dose is divided into two doses for safety reasons [27].

12.3.2.2 Nasal Aspirin Challenge

Nasal aspirin challenge is safer and may be considered in patients with severe asthma in whom oral or bronchial aspirin challenges are contraindicated. This type of provocation may be supervised in a hospital outpatient clinic. Before the challenge, all patients should undergo rhinological examination with anterior rhinoscopy to evaluate the presence of nasal polyps. Any pathology of the nasal cavity, such as septal perforation or massive nasal polyposis which could influence the outcome of nasal aspirin challenge, is a contraindication to the nasal challenge procedure. A stabilisation period of at least 30 min should precede the nasal aspirin challenge to exclude the influence of environmental factors on nasal hypersensitivity [27].

At baseline nasal symptoms, inspiratory flows and nasal volumes are recorded during the first 30 min at 10-min intervals. Then the nasal challenge with 0.9% NaCl (80 μL) instilled into each nostril via an Eppendorf pipette is carried out for assessment of nonspecific nasal hyperreactivity. Nasal symptoms, inspiratory flow and nasal volumes are measured over the following 30 min at 10-min intervals. If a change over 20% in the recorded values occurs, then the upper airway is hyperreactive and further challenge could not take place. Finally L-ASA 80 μL (total aspirin dose—16 mg) is instilled (using an Eppendorf pipette) into each nostril with the patient's head tilted back for 1 min. Following L-ASA (80 ll) administration, nasal symptoms, inspiratory flow and nasal volumes are measured in the following 2 h at 10-min intervals. In patients who develop clinical symptoms by the end of 2 h of observation, nasal symptoms, inspiratory flow and nasal volumes are measured throughout the following hour (third hour following L-ASA administration) at 10-min intervals [27].

An alternative protocol uses gradually increasing doses of intranasal lysine aspirin, with at least 45 min between each dose [29]. The usual provoking dose is 15–30 mg.

A positive reaction to nasal aspirin challenge is defined as the appearance of nasal symptoms such as rhinorrhoea, nasal congestion, sneezing and 25% decrease of total nasal flow value at 12 cm, as compared with baseline measured by acoustic rhinometry, or 40% bilateral drop of inspiratory nasal flow, as compared with the baseline value assessed by rhinomanometry or PNIF meter. Nasal alpha-mimetics (e.g. topical oxymetazoline) are used to treat nasal obstruction following nasal aspirin challenge. In the case of severe nasal adverse reactions, oral corticosteroids may have to be administered. A negative nasal challenge should be followed by oral challenge to rule out aspirin sensitivity beyond reasonable doubt [27].

12.3.2.3 The American Experience

Two guidelines produced following experience of over 1500 AD procedures conducted at the Scripps Clinic on N-ERD sufferers have been reported. It takes on average 102 min between receiving the oral dose of ASA and having a reaction. Usually, the dose of aspirin that causes the reaction is in the range 45–100 mg. On this basis, doses are provided three-hourly [30]. A hybrid procedure using ketorolac intranasally initially (since lysine aspirin is not obtainable in the USA) makes a saving in time, such that a day and a half is sufficient rather than the usual 3–4 days. However, its use is confined to cases without polyps that block the nose [31, 32]. The most usual type of reaction (90%) is naso-ocular and then symptoms affecting the bronchi or larynx (43%). Responses occurring outside the respiratory tract are less common: gut (23%) and skin (10%) [33]. Symptoms affecting the bronchi or larynx may be treated with salbutamol or racepinephrine, and then the ASA dosage repeated. Where reactions only affect the nasal lining, oxymetazoline and azelastine, either separately or in combination, may be supplied intranasally, and the next stepped dosage given. The Scripps Clinic saw 1500 cases for AD, of which only three individuals had a systemic reaction. In these cases, intramuscular adrenaline was provided and admission to hospital was not required [26].

12.3.2.4 Aspirin Treatment After Desensitisation (ATAD)

Aspirin desensitisation (ATAD) has emerged as a treatment suitable for treatment-refractory asthma of severe degree necessitating the use of steroids or with formation of polyps in the nose. ATAD does not work in nonaspirin-sensitive subjects [34].

Multiple studies have been able to show clinical benefit from ATAD. Most such studies were open label and not placebo-controlled [35], but a recent trial featured double blinding and employed placebo [36].

ATAD has efficacy in managing N-ERD and is a safe procedure. Following its introduction in 1979, the benefit from ATAD has been shown on multiple occasions in a research setting. Research outcome measures have included annual sinus infection count, olfactory scores, nasal symptom scores, asthma symptom scores, sinus operative procedures, admission to hospital and attendance at accident and emergency. The trials employed an observational and retrospective methodology [37]. The need for

prednisolone on a daily basis also reduced by approaching 70% following ATAD [5]. Up to now, seven RCTs have been undertaken to examine the benefit of ATAD, of which six proved the efficacy [38–44]. The most current trial involved 34 individuals given aspirin 650 mg b.d. over a 6-month period. The trial featured random allocation and placebo control, and both the researchers and trial subjects were blinded. Benefit was demonstrated at the level of statistical significance in FEV1, SNOT-22, symptomatic score, medication score and Lund-Mackay CT scoring [38].

ATAD is achievable in a sufficiently safe fashion in an outpatient department (not oral, only nasal), provided patient observation is possible by trained healthcare personnel and doctors. Although there are standardised guidelines available for ATAD, how much aspirin to prescribe depends on individual patient factors [30]. Earlier research had dose ranges between 300 and 2600 mg daily [45], but more recent findings suggest that a dose of 650 mg has the same effect as 1300 mg, and even a dose of 300 mg daily is clinically efficacious [40, 42, 46, 47]. Cases of N-ERD (NSAID-exacerbated respiratory disease) usually necessitate a starting dose between 10 and 20 mg greater than that used in CAD (coronary artery disease) cases (0.1–10 mg) [40, 42, 46, 47]. The majority of hypersensitivity reactions that take place in ATAD, both upper and lower respiratory tracts, happen when the dose is between 40 and 160 mg [40, 42, 46, 47].

Different hospitals recommend different ways to approach ATAD, but a common feature is an initial dose by mouth at the low end (30 mg) and increasing towards 650 mg over the course of 2–3 days, if tolerated by the patient. A popular method is to use both aspirin by mouth, at an adjusted dosage, and ketorolac by nasal application (so-called “hybrid” technique), allowing the protocol to be completed within 48 h [48].

The majority of N-ERD sufferers would benefit from ATAD; however, there are some patients who cannot tolerate ATAD because of associated symptoms affecting the skin, gut or lungs. Laidlaw et al. tried to identify the features that characterise the group at risk of not tolerating ATAD. The at-risk group had features of dysregulation in the prostaglandin-associated pathways, with notably elevated levels of PGD2. This could be demonstrated in both urine and blood. There was a correlation between the PGD2 level and how severely the airway became obstructed when a reaction occurred [49].

That ATAD is efficacious in cases of N-ERD has been demonstrated on several occasions by researchers. The treatment leads to amelioration in symptoms with corresponding increase in quality of life, lessened polyp growth in the nose, less sinusal infection, decreased prescription of glucocorticoids by mouth and fewer operations on the sinus [36, 47, 50]. The benefit in nasal and asthma scores and olfactory function emerge in the first month [51]. A Cochrane meta-analysis is proposed [52].

How ATAD functions is largely unknown. Early studies involved small numbers of participants and could not definitively show alteration in how the eicosanoids were metabolised. However, subsequent studies have shown [53, 54] that prolonged ATAD inhibits the production of IL-4 through actions on the STAT 6 (transcription 6 signalling) pathway and have demonstrated that markers of Th1 activity were increased. The action on STAT 6 involves inhibiting tyrosine kinases that phosphorylate the transducers and activators within the pathway [53, 54].

Whilst the way continuous ASA treatment affects the underlying pathophysiology is unknown, metabolic derangement of arachidonic acid metabolism in N-ERD undergoes rebalancing straightaway, resulting in lowered expression of cysteinyl leukotrienes and the corresponding receptors [13], plus long-lasting suppression of leukotrienes [13, 55].

12.3.3 Maintenance Dose of Aspirin

The ideal oral dose of ASA has not been ascertained. ASA at a high dose (i.e. 650 mg b.d.) is known to be effective in the management of respiratory disease in cases of N-ERD [30, 54]. Research that contrasted doses of 325 vs 650 mg b.d. discovered around half of the patients were adequately treated on 325 mg b.d., but the remainder needed a total daily dose of 1300 mg. The authors propose an initial dose of 650 mg b.d. to continue 1 month, then reducing by 325 mg each month, titrating the dose against the patient response. For individuals who are taking cardioprotective NSAIDs, the dose should be no lower than 325 mg, as such a dose will facilitate cross-tolerance to any NSAID inhibiting COX-1. It may be insufficient for respiratory disease, however [40].

12.3.3.1 Side Effects

ATAD may be associated with adverse effects including gastrointestinal irritation, rush, urticaria epistaxis and worsening of nasal or bronchial symptoms [56].

After ATAD occurs, the refractory period lasts 2–3 days. Continuous treatment maintains the tolerance. However, where more than 4 days have elapsed since the administration of aspirin, desensitisation warrants repeating [57]. Where a period of between 3 and 4 days has elapsed since taking aspirin doses, the patient needs to return to the clinic for a supervised dose of aspirin 325 mg stat.

The usual nasal dose is 75 mg aspirin once daily [58], but some patients improve on lower doses, and clinical benefit was demonstrated at 30 mg [59].

Reduction in leukotriene receptors occurred at 16 mg daily [13].

Side effects on nasal lysine aspirin are few, less than with oral aspirin [58]. Patient concordance with this long-term therapy requires continued clinician input and monitoring.

The use of ATAD in managing N-ERD is safe, clinically efficacious and much cheaper than the use of monoclonal antibodies such as omalizumab, mepolizumab or dupilumab, so it should be tried if possible before such treatments are instigated [26].

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Complementary and Alternative Medicine in Allergic Rhinitis

13

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13.1 Introduction

Complementary and alternative medicine (CAM) was defined by the National Center for Complementary and Alternative Medicine (a branch of the National Institutes of Health) as a group of diverse medical and health-care systems, therapies, and products that are often not integrated with conventional medicine. Worldwide, there are a large number of CAM therapies that vary by country, religion, race, history, and culture. CAM therapies have been used by more than 80% of the world's population, and this number has been increasing throughout the world. In public opinion surveys, the rate of CAM usage among the general population was reported to be 49% in France, 26% in the United Kingdom, and 46% in Germany [1]. In the United States, the use of at least one alternative therapy increased from 33.8% in 1990 to 42.1% in 1997 with out-of-pocket expenditures of around $27.0 billion [2].

For chronic diseases, patients tend to seek treatment modalities outside of conventional medicine, and CAM therapy has become increasingly common among these patients [3, 4]. The use of CAM therapies is also prevalent among asthma and allergic rhinitis (AR) patients with a reported rate of 42% in the United States [5]. In this chapter, we review the more commonly used allergic rhinitis complementary and alternative therapies.

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_13

13.2 Herbal Therapy

Herbal therapy is a frequently preferred treatment modality for allergic rhinitis by patients who are dissatisfied with conventional treatment modalities. Numerous studies have investigated the efficacy and safety of herbal agents in the management of AR. In the 2018 International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR: AR), recommendation for use of herbal products in AR was thought unlikely, since the relevant published literature was found to be of poor quality and it included too small a study population [6]. We have reviewed a number of studies, mostly composed of randomized controlled trials (RCTs) or experimental work, and summarize the reported efficacy of allergic rhinitis management with herbal remedies.

Chinese herbal medicine (CHM) is a frequently sought-after option for patients with AR seeking complementary and alternative therapy. In traditional Chinese medicine, the principle of disease treatment is based on syndrome differentiation or pattern identification. Qi deficiency syndrome is a traditional Chinese medicine concept that relies on the balance of energies in the body as determinants of health and well-being. In the studies we identified, the vast majority of patients with AR were believed and reported to have lung and spleen qi deficiency syndrome, and treatments therefore revolved around strengthening the lung and spleen energies [7]. In a recent meta-analysis, Zhang et al. [8] evaluated the results of 11 randomized controlled trials comparing the benefit of CHM versus placebo for the treatment of patients with AR and reported that CHM seemed to provide improvement in the quality of life of AR patients compared with both placebo and traditional AR medicines. However, in this review, there was no significant difference in terms of sneezing and total nasal symptom scores between CHM and placebo or some conventional treatments. In a previous meta-analysis, Wang et al. [9] reported that CHM provided a significant reduction in total nasal symptom scores in AR patients compared to placebo according to seven reviewed randomized controlled trials. These discordant findings are possibly due to the limited number of studies and multiple heterogeneities within the trials. It seems that further multicenter and well-controlled studies with a larger patient population may assist in determining the real potential of CHM. *Yu ping feng san* (YPFS), a CHM formula composed of three major herbs, *Astragalus membranaceus* (huang qi), *Rhizoma Atractylodis Macrocephalae* (bai zhu), and *Radix Ledebouriellae Divaricatae* (fang feng), was a recommended agent to treat AR according to the Chinese medicine clinical practice guideline. However, in a systematic review and meta-analysis of 22 randomized controlled trials regarding the effectiveness of YPFS in AR, Luo et al. demonstrated that the benefit of YPFS was not superior to pharmacotherapy, but the YPFS and pharmacotherapy combination therapy appeared to be more effective than pharmacotherapy alone [10]. According to this meta-analysis, combination therapy lasting for more than 3 weeks seemed to be more effective with an adequate safety profile. In conclusion, the authors also indicated that the included studies had low methodological quality and recommended further RCTs utilizing widely accepted outcome measures. *Bu zhongyi qi tang* (BZYQT), another CHM formula composed of nine herbs, has been

suggested to be effective for patients with perennial AR due to its anti-inflammatory effect. Yang and Yu [11] demonstrated that BZYQT treatment of AR reduced nasal symptoms with the suppression of total serum IgE, interleukin-4-stimulated prostaglandin E2, and leukotriene C4 production, as well as COX-2 mRNA expression by polymorphonuclear neutrophils.

Aller-7 is a polyherbal product containing a mixture of seven herbal extracts: *Albizia lebbeck*, *Phyllanthus emblica*, *Piper longum*, *Piper nigrum*, *Terminalia bellerica*, *Terminalia chebula*, and *Zingiber officinale*. The mixture has anti-inflammatory, antioxidant, antihistamine, antispasmodic, and mast cell stabilization activities that have been demonstrated in experimental studies. According to a multicenter controlled trial, Aller-7 exhibited a significant decrease in nasal symptoms of AR with a significant improvement in mucociliary clearance time, absolute eosinophil count, peak nasal flow rate, and peak expiratory flow rate [12]. Also, no serious adverse event was seen in AR patients treated in this study, and the authors concluded that Aller-7 is efficacious and well tolerated.

Besides the CHM agents, there are also several alternative herbal products that have been used for AR. Japanese cedar pollinosis is one of the most prevalent causes of seasonal allergic rhinitis (SAR) in Japan. The effectiveness of regular Benifuuki green tea containing *O*-methylated epigallocatechin-3-*O*-(3-*O*-methyl) gallate consumption for about 6 weeks before the initiation of the pollen dispersal season was compared with placebo in terms of preventing AR symptoms [13]. The study found that Benifuuki green tea significantly reduced rhinoconjunctival symptoms as well as improved the quality of life scores in patients with Japanese cedar pollinosis. Also in an experimental study, the anti-inflammatory effect of green tea containing epigallocatechin gallate was investigated on ovalbumin-induced AR and showed that administration of epigallocatechin gallate decreased serum IgE and histamine, nasal fluid interleukin-1β (IL-1β), IL-4, and IL-6 and inhibited the nasal mucosa mRNA and protein expression of cyclooxygenase 2, IL-1β, IL-4, and IL-6 while significantly diminishing the number of sneezes and the occurrence of nasal rubbing [14].

Butterbur (*Petasites hybridus*) is an herbaceous plant in the Asteraceae family and has been extensively investigated in the management of asthma and AR. Butterbur was shown to inhibit type 1 hypersensitivity reaction by suppressing leukotriene and histamine biosynthesis and mast cell degranulation. Three randomized, double-blind, placebo-controlled (RDBPC) trials revealed that butterbur provided symptom relief in AR patients without exhibiting a sedative effect [15]. Lee et al. [16] reported that butterbur was as effective as fexofenadine in attenuating the nasal response to adenosine monophosphate and in alleviating nasal symptoms in the treatment of AR. Also, the effect of butterbur was found to be similar to that of cetirizine in the treatment of SAR according to the blinded evaluation of both patients and doctors. Therefore, it is suggested as an alternative option in conditions in which the avoidance of the sedative effect of antihistamines is required [17]. However, fexofenadine is itself nonsedating.

Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is the pungent component of chili peppers, which are plants of the genus *Capsicum*. Intranasal capsaicin was

shown to block neuropeptides (mostly substance P) and reduce nasal hyperresponsiveness. Capsaicin initially irritates the application areas, and subsequently the area becomes desensitized to the irritation after repeated use. The efficacy of intranasal capsaicin spray was evaluated in different pathologies and suggested that repeated usage may be beneficial for symptoms of chronic rhinitis including nasal obstruction, rhinorrhea, and sneezing [18]. However, a Cochrane Review published in 2006 revealed that there was not adequate evidence to evaluate the usage of capsaicin in the treatment of AR [19].

Oral or topical administration of *Nigella sativa*, also known as black seed or black cumin, was reported to provide symptom alleviation for patients with AR. The antiallergic activity of *N. sativa* was suggested to be due to its active ingredient, thymoquinone, with carbonyl polymer. Nikakhlagh et al. [20] reported that oral *N. sativa* administration could reduce nasal symptoms including congestion, itching, and sneezing as well as mucosal pallor during the first 2 weeks. Also, Alsamarai et al. [21] showed the benefit of topical nasal administration of black seed oil in the treatment of AR with a high safety profile. Işik et al. [22] demonstrated that black seed oil supplementation during subcutaneous allergen-specific immunotherapy appeared to have beneficial effects on AR symptoms and may be used as adjuvant therapy.

Perilla frutescens is a dietary leaf herb that has been reported to have antiallergic and anti-inflammatory activity. The benefit of oral supplementation of *Perilla frutescens* extract enriched for rosmarinic acid was investigated in patients with seasonal allergic rhinoconjunctivitis in a RDBPC trial [23]. The study demonstrated that it could be an effective treatment modality for patients with mild SAR and might reduce treatment costs as an alternative treatment. In a recent study, a new *Perilla frutescens*-derived flavanone derivative (*Perilla*-derived methoxyflavanone, PDMF) potently inhibited IgE-induced immediate hypersensitivity reactions and also prevented AR-like nasal symptoms in a murine model of Japanese cedar pollinosis [24].

Quercetin is a member of the flavonoids that has several beneficial biological activities such as antioxidant, antiproliferative, antidiabetic, and antiallergic activities. In an experimental study, quercetin was shown to be effective in ovalbumin-induced AR both histopathologically and serologically [25]. In this study, quercetin-administered rats had lower total and ovalbumin-specific IgE levels with decreased eosinophil infiltration, vascular and secretory gland dilatation, and COX-2 and VIP expression compared to the control group. Kashiwabara et al. [26] demonstrated that oral administration of quercetin to toluene 2,4-diisocyanate-sensitized rats for 5 and 7 days could suppress sneezing and nasal rubbing movements with the inhibition of substance P, calcitonin gene-related peptide, and nerve growth factor contents in nasal lavage fluids. Hence, the authors suggested that quercetin could be a good candidate as a supplement in the treatment of AR. The underlying mechanisms of the clinical efficacy of quercetin in AR were also investigated in some studies. Edo et al. [27] reported that quercetin had an ability to increase thioredoxin, an endogenous antioxidant protein. Thioredoxin was reported

to have an immunomodulatory effect and was able to provide allergic response prevention with the suppression of oxidative stress responses in the nasal mucosa. Also, Ebihara et al. [28] reported that quercetin had the capability to change the clinical course of AR by reducing nitric oxide production from nasal epithelial cells after IL-4 stimulation. However, the data on the efficacy of quercetin in AR were mostly derived from experimental studies and require more clinical work in patients with AR.

Spirulina is a biomass of cyanobacteria (blue-green algae) that has been eaten by humans for hundreds of years. Spirulina has been used to treat many diseases including AR. Cingi et al. [29] evaluated the effectiveness and tolerability of spirulina in the treatment of AR in a RDBPC study. The authors demonstrated that spirulina improved the symptoms including nasal congestion, sneezing, nasal discharge, and itching with good patient compliance when compared with placebo. Also, it was shown that spirulina had an immunomodulatory effect such as suppression of Th2 cell differentiation, inhibition of IL-4 production, and decrease of serum histamine and IgE levels [30].

TJ-19 (Sho-seiryo-to, Xiao-Qing-Long-Tang, So-Cheong-Ryong-Tang) is a Korean mixed herbal formula that has been used in the treatment of the common cold, bronchitis, allergic asthma, and AR. TJ-19 was reported to be the most preferred medicine for the treatment of AR by the specialists in the Department of Otorhinolaryngology of Traditional Korean Medicine. Experimental studies revealed that TJ-19 was effective for suppressing the progression of AR and allergic asthma. A recent animal study reported that TJ-19 decreased mast cell infiltration into the nasal cavity and reduced the serum levels of IL-4 and leukemia inhibitory factor LIF [31]. Also, TJ-19 was found to inhibit the level of TNF-α and IL-6 in splenocytes in this study, and the authors concluded that TJ-19 might be effective in the treatment of AR. A RDBPC study demonstrated that TJ-19 significantly improved the nasal symptoms of perennial allergic disease (PAR) including nasal discharge, sneezing, and stuffy nose [32].

Urtica dioica (stinging nettle) is an herbaceous perennial flowering plant belonging to the family of Urticaceae, genus *Urtica*. *Urtica dioica* was shown to inhibit inflammatory events such as inhibition of prostaglandin formation by suppression of cyclooxygenase-1, cyclooxygenase-2, and hematopoietic prostaglandin D2 synthase, central enzymes in pro-inflammatory pathways that have a role in the occurrence of SAR symptoms. Also, *Urtica dioica* had antagonist and negative agonist activity against the histamine-1 receptor as well as inhibited mast cell tryptase [33]. The first RDBPC study investigating the benefit of *Urtica dioica* in the treatment of AR was published by Mittman in 1990 [34]. According to daily symptom diaries and global response, 58% of the participants benefited from *Urtica dioica* in terms of symptom relief after 1 week of therapy. In a recent study, Bakhshaee et al. [35] investigated the effect of *Urtica dioica* on clinical and laboratory signs of AR in a RDBPC study. The authors showed certain positive effects of *Urtica dioica* in AR patients; however, the results were ultimately similar to placebo effects.

13.2.1 A Note of Caution

Herbal remedies do not conform to the same high standards as prescription medications. Batches may not be uniform and may or may not contain any active extract. Some Chinese herbal preparations have found to have been adulterated with corticosteroids. In addition, herbal medicines can have adverse effects, especially upon the liver, and can interact or interfere with important prescribed medications, such as warfarin.

13.3 Acupuncture

Acupuncture is one of the oldest therapeutic modalities that has been utilized in several diseases for thousands of years. Acupuncture is performed by special needles that penetrate to certain acupuncture points. The conceptual theory of acupuncture relies on the vital energy of the body that flows through a network of meridian lines beneath the skin. Along the meridians, there are specific anatomic locations called acupoints that are suggested to correspond to the flow of energy through the body. During pathological conditions, the flow of the body's vital energy is impaired, and acupuncture aims to stimulate acupoints with needles to rebalance the energy flow [36].

Acupuncture has been performed to heal numerous diseases due to its low adverse effect profile, practical application, and low cost. Acupuncture therapy has been suggested as an efficient treatment method in patients with AR according to several RDBPC trials. Chen et al. [37] compared real versus sham acupuncture in 140 patients with PAR or seasonal allergic rhinitis (SAR) and showed the benefit of acupuncture in treating AR. In 2018, Adam et al. [38] reported that the antihistamine intake was significantly lower in SAR patients treated with acupuncture than in patients having a sham acupuncture group or rescue medication alone. Also, in this study, acupuncture appeared to improve rhinitis-specific quality of life and SAR symptoms. However, two meta-analyses evaluating the efficacy of acupuncture therapy in AR demonstrated conflicting results. In the first meta-analysis published in 2008, it was stated that acupuncture had no overall effects on AR symptom scores or use of medication [39]. A more recent meta-analysis, however, demonstrated that AR patients who received acupuncture therapy had a significant reduction in nasal symptoms, improvement in the rhinitis-specific quality of life scores, and reduced need for rescue medications [40]. According to the 2018 ICAR: AR, the benefit of acupuncture was stated as unclear in AR; however, it is suggested as a possible therapeutic adjunct in patients who wish to avoid medical therapy [6].

Although the exact underlying mechanisms have not yet been completely elucidated, the efficacy of modern acupuncture is proposed to be related to its anti-inflammatory effects. Accordingly, a recent systematic review and meta-analysis revealed that AR patients treated with acupuncture had significantly decreased serum IgE along with reduced nasal symptoms and medication scores [40]. McDonald et al. [41] found a significant decrease of total IgE and house dust

mite-specific IgE after 16 sessions of real acupuncture treatment. Petti et al. [42] showed a significant reduction in serum IL-10 levels in patients with AR who had acupuncture therapy. In an experimental AR model, warm acupuncture was shown to inhibit the expression of serum IgE, IL-1β, and TNF-α [43]. Mi et al. [44] investigated the effect of acupuncture at the sphenopalatine acupoints in PAR and demonstrated a significant benefit in the prevention of PAR. The authors reported that stimulating the sphenopalatine ganglion acupoint decreased nasal hyperresponsiveness by means of lowering the sensitivity of the nasal sensory nerves, establishing a balanced autonomic nervous system, and downregulating the central nervous system sensation. Although these findings suggest an immunomodulatory effect of acupuncture in the treatment of AR, future work is required in order to elucidate the clinical significance of these changes.

13.4 Honey

Honey and honey bee products have been used for therapeutic purposes for various diseases including allergic disorders in many countries, cultures, and religions since ancient times. However, the underlying mechanism of the antiallergic effect of honey and its products remains to be elucidated. In 1997, Duddukuri et al. [45] reported that ovalbumin-specific IgE antibody responses were suppressed by honey in rats and suggested honey as a treatment modality in pathological conditions requiring immunosuppression. Ishikawa et al. demonstrated that bee pollen exerted an antiallergic effect via inhibition of the Fc epsilon RI-mediated activation of mast cells that acts in the early and late phase of allergic reactions [46]. In the latest study of Ishikawa et al. [47], the authors measured the activation of cutaneous mast cells by using a passive cutaneous anaphylaxis reaction and showed that IgE-induced mast cell activation was decreased by oral administration of bee pollen to mice. Shaha et al. [48] demonstrated that the number of sneezes was decreased in toluene 2,4-diisocyanate-stimulated rats by treatment with honey bee products of royal jelly and Brazilian green propolis. Along with the improvement of nasal symptoms, a remarkable suppression of histamine H1 receptor (H1R) mRNA and nuclear factor of activated T-cell (NFAT)-mediated IL-9 gene expression were observed in the nasal mucosa in this study. H1R receptor is the main pathway for histamine-mediated allergic and inflammatory reactions. IL-9 is a pleiotropic cytokine that promotes Th2-specific allergic responses, and NFAT-mediated IL-9 gene expression is one of the important signal pathways attributed to the development of AR [49].

One might wonder why so much animal work is necessary since administration of honey to man is unproblematic.

Studies investigating the benefit of honey in the treatment of AR revealed conflicting results in the literature. Rajan et al. [50] reported no effect of honey on symptom improvement in patients with allergic rhinoconjunctivitis when compared with the placebo group. In a study conducted on patients with birch pollen allergy, Saarinen et al. [51] treated patients with either birch pollen honey or regular honey and assessed the effects of pre-seasonal use of these agents on symptoms and

medication during the birch pollen season. Birch pollen honey showed significantly better symptom control than conventional medicine among affected patients, and the authors concluded that it could be a complementary therapy for birch pollen allergy. However, in this study, total symptom scores including nasal, conjunctival, and skin symptoms did not differ between the patients administered birch pollen honey and regular honey. Asha'ari et al. [52] investigated the complementary effect of a high dose of honey on 40 patients with AR. All patients received a daily dose of 10 mg of loratadine for 4 weeks and were randomly divided into two groups. The case group ingested 1 g/kg/day honey, whereas the control group ingested a placebo syrup. The results of the study demonstrated that the overall and individual AR symptoms were improved in the case group and suggested that honey ingestion appeared to be a complementary treatment modality for AR.

Ernst has expressed concerns about CAM research including the fact that it is generally of poor quality and published mainly in two journals [55]. Uncritical acceptance of CAM as more natural and less harmful than prescription medicines is unwarranted [53]. The ARIA guidelines [54] state that the methodology of clinical trials with complementary-alternative medicine was frequently inadequate. Meta-analyses provided no clear evidence for the efficacy of acupuncture in rhinitis and asthma. Some positive results were described with homeopathy in good-quality trials in rhinitis, but a number of negative studies were also found. Therefore it is not possible to provide evidence-based recommendations for homeopathy in the treatment of allergic rhinitis, and further trials are needed. A limited number of studies of herbal remedies showed some efficacy in rhinitis and asthma, but the studies were too few to make recommendations. There are also unresolved safety concerns. Therapeutic efficacy of complementary-alternative treatments for rhinitis and asthma is not supported by currently available evidence.

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14 Sneezing and Nasal Discharge as a Barrier in Communication During Adolescence

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14.1 Introduction

Allergic rhinitis (AR) for the most part initially occurs in early childhood and is the result of hypersensitivity to specific allergens, which trigger an IgE-linked inflammatory reaction in the lining of the nose. Although any patient above the age of 2 years may become sensitized to allergens in the outdoor environment, the highest incidence is in the group aged 14–16 years. Indoor allergens, by contrast, may cause children to present clinically even before the age of 2 years, the most frequent culprits in such cases being allergens found in dust mites, pet dander, cockroaches, moulds and pollen [1].

14.2 Pathophysiology

AR is triggered by an IgE-linked response to any of several allergens that come into contact with the lining of the nose. The most frequent allergens come from dust mites, pet dander, cockroaches, moulds and pollen. Tree pollen contains epitopes that IgE attaches to. The IgE is found on the outer cellular membrane of mast cells, where it is bound to the Fcε receptor. Degranulation occurs when two immunoglobulins attach to the allergen and thereby cross link. The subsequent inflammatory cascade then accounts for the symptomatic constellation recognizable as AR. The symptoms include sneeze; blocked nose; nasal

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_14

stuffiness; nasal discharge; coughing; nasal, ocular and pharyngeal pruritus; sinus pressure; headaches; and nosebleeds [1].

The range of antigens present outside depends on the season and geographical location. A knowledge of the seasonal prevalence of particular antigens assists in the identification and management of AR, as well as allowing allergy to be excluded in certain cases. To take a concrete example, a case of blocked nose in a clinic in Boston (USA) in November cannot be explained as AR secondary to tree pollen, as the allergen prevalence does not fit the time of presentation.

An inflammatory response usually occurs in both the proximal and distal portions of the airway (i.e. nasal and pulmonary airway) as a result of contact with allergen. It is widely accepted that the airway is best understood as a functional entity rather than as a discrete organ. It has been found that the majority of asthmatic individuals also suffer from AR. Indeed, there are specific guidelines in existence for managing asthma where AR is also present [2]. If an allergen initiates an inflammatory response in the proximal airway, distal airway symptoms may also occur, as well as the converse. One study indicated that asthmatic individuals with uncontrolled AR have double the risk of attendance at accident and emergency and triple the risk of hospital admission for an asthma attack [3]. It has likewise been shown how therapy for asthma improves AR and vice versa.

14.3 Signs and Symptoms

Cases of AR may present with classical or atypical symptoms. Whilst a history of classical AR symptoms that began when a new pet entered the home or that coincide with the pattern of a seasonal allergy readily leads to a diagnosis of AR, in a young child with AR, there may be more subtle indicators, and nasal stuffiness may pass unremarked, albeit the persistent nasal blockage is evident to the relatives. On occasion, hay fever may be wrongly diagnosed when the cause is in fact an allergy to pet dander, which typically falls from the animal in spring and builds up again during the autumn. An older child occasionally seems less severely affected than is really the case because of having developed coping skills to deal with the symptoms [1].

AR in children may produce signs and symptoms as follows [1]:

- Rhinorrhoea, blocked nose, postnasal drip
- Pallor of the turbinates in the nose, sometimes involving a clear discharge from the nose
- Repeated sneezing
- Nasal, palatal, ocular and ear pruritus
- Snoring
- Frequently occurring painful throat
- A need to keep clearing the throat, coughing
- Headaches

14.4 Sneezing

Sneezing (sternutation) generally serves to protect the airway but may also indicate a variety of disorders. Sneezing has been commented on since ancient times. There are many cultures and regions within Eurasia where sneezing is associated with superstitious beliefs and said to forebode something. Besides its ability to protect the airway, knowledge about sneezing is limited. Sternutation involves forcibly evacuating air from the lungs orally or nasally, and the reflex is most often triggered by the lining of the nose becoming irritated. Being suddenly exposed to strong light, having a very full stomach, physical stimuli to the fifth cranial nerve and disease of the central nervous system (e.g. epilepsy, posterior inferior cerebellar artery syndrome) or psychological disturbance may all trigger the urge to sneeze [4].

Sneezing is a two-part reflex action. The first part is the nasal phase, involving sensory fibres which fire in response to physical or chemical irritation to the lining of the nose. The terminal branches of the fifth cranial nerve have their endings in the skin of the face and supply the sensation of touch, pain and temperature, with a few fibres innervating the mucosa of the nose [5]. The sensory nerves are slender and ensheathed in myelin, ending in a sensory receptor. The types of sensory stimuli that can be detected include chemical, tactile and mechanical [5]. Afferent neural supply is from the anterior ethmoidal, posterior nasal and infraorbital divisions of the fifth cranial nerve and terminates in the trigeminal ganglion [6]. Signals relayed from the trigeminal ganglion pass to the sneezing centre within the lateral medulla [7]. When the stimulatory threshold has been exceeded, the second part of the reflex comes into play. This part is termed the “respiratory” or “effector” arc. Neurones responsible for both inspiration and expiration are involved [8]. The eyes are shut, and the air is drawn in deeply and then forcefully evacuated, at the beginning against resistance from a closed glottis. Pressure within the lungs rises. When the glottis abruptly relaxes, an explosive puff of air occurs out of the lungs, via the mouth and nose, clearing away any particles or irritant substances that have gathered on the mucosae [4].

14.5 Effect of Allergic Rhinitis on Communication

Atopic disorders involving IgE (such as allergic rhinoconjunctivitis, atopic asthma and food allergy) are present at a frequency approaching 30% in the general population. This prevalence is growing in developed countries. Infants and younger children also frequently suffer from food allergies not related to IgE sensitization. Atopic disorders are most evident when they provoke particular physical symptoms, but they can also produce less obvious symptoms, of a neuropsychiatric type, e.g. making children more hyperactive or irritable [9].

Clinicians have often observed that emotional distress can worsen the severity of atopic disorders, but this has now been shown in research involving the effect of mood and psychological stress on atopic disease. Gauci et al. discovered that scores

on the Minnesota Multiphasic Personality Inventory correlated with the level of skin reaction observed when allergen challenge was performed [10]. Other research has also demonstrated that being hospitalized for an asthma attack was more common when a significant life event occurred, supportive frameworks were weak or a mood disorder was present [11]. Additionally, adverse life events and overthinking with a negative focus also lead to worsening of asthma [12, 13].

Given that AR features among the most frequent of chronic disorders and is a problem on a worldwide scale, consideration of how it affects communication is of key interest. AR has effects on the sufferer's day-to-day life. Patients are frequently symptomatic, and therapy is long-standing. To manage the disorder adequately to provide a good quality of life, there is a need for prevention of contact with the allergen, pharmacotherapy and occasionally immunotherapy. The running nose and blocked nose may lead to headaches and insomnia and may adversely affect learning [14].

Individuals with AR also exhibit particular behavioural signs. The "nasal salute" or "allergic salute" consists of an action designed to prevent nasal discharge and provide relief from pruritus. The effect of AR on mental health is most apparent in individuals with pre-existing psychological or emotional issues or mood disorders. A raised prevalence of depression, social introversion and impaired psychological function has been identified in allergic rhinitis sufferers. Communication skills in patients with AR are subject to three types of alteration: physiological, psychological and behavioural. Since AR can result in an alteration in all three dimensions of the communication process, it may entail emotional, mental and physical barriers to effective communication [14].

Cingi et al. [15] investigated the negative impact on social communication experienced by patients with AR in young adulthood. Communication involves the transfer of information, feedback or responses, ideas and feelings [16]. It is a process that needs to occur on a daily basis. Communication may involve the use of words or other types of signal. For communication to be highly effective and to achieve the goal of furthering positive relationships between people, both verbal and non-verbal elements of the process must interact effectively [17]. Research has explored the extent of interaction between the type of personality and AR, particularly in females, and indicates that AR is most likely to be at least of moderate degree in individuals whose personality traits include neuroticism, depression, social anxiety and shyness [18].

Since problems with AR are most likely to occur with young children who are early in their developmental processes of establishing relevant social skills, it is important to recognize the serious influences that this health problem can have on establishing important interpersonal communication competencies [19]. Communication competence is a critical factor in effective relationship development, interpersonal coordination and the ability to promote social organization throughout life [20]. The physiological and psychological alterations that have been related to AR are very likely to complicate the development of important interpersonal communication and behavioural skills that children engage in and establish a precedent for threatening their overall communication competence. The association

of rhinitis with poor hearing and otitis media with effusion [21] means that listening, hearing and speech development may all be impacted (see Chap. 18). This includes impeding their abilities to initiate conversations with others, disclose relevant information and develop/maintain meaningful interpersonal relationships [22]. Children's development of these central communication competencies can be especially relevant for establishing and maintaining effective interpersonal relationships throughout their lives, within their families, schools, workplaces, social organizations and communities, even influencing the quality of their healthcare relationships with caregivers [23]. The Relational Health Care Competence Model suggests that the development and expression of interpersonal communication competencies are essential for enhancing interpersonal coordination, cooperation and information sharing, enabling the achievement of important individual and collective goals, such as enhancing the quality of health outcomes [24]. It is imperative that parents and healthcare providers recognize the kinds of developmental communication deficiencies that are likely to be associated with AR in young children, so that remediation efforts can be afforded to these children to help them overcome these interpersonal communication competence problems.

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How Should Rhinitis Be Managed During Pregnancy?

15

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15.1 Introduction

Diagnosing and managing rhinitis, sinusitis and nosebleeds in pregnant women is a particularly difficult task for ENT specialists. On one hand, disorders of the nose and sinuses, when not adequately treated, present risks to the quality of life of the woman and endanger the pregnancy, and on the other hand, data regarding the safety aspects from properly controlled trials are simply lacking [1].

The rhinological impacts on pregnancy include rhinitis of pregnancy, nosebleeds and particular tumours, e.g. pyogenic granuloma. These conditions have been written about previously [2–6]. There are also case reports that have appeared from time to time, concerning how rhinosinusitis may interact with pregnancy [7–9].

15.2 Rhinitis of Pregnancy

Pregnancy rhinitis is a condition in which the nose becomes congested in the final month or 2 months before delivery, but with no further indications of infection within the respiratory tract and no allergic response and with complete resolution in less than 2 weeks after giving birth [10–12].

Physiological changes brought about by pregnancy include the lining of the nose becoming hyperaemic and oedematous. The physiological consequences of pregnancy on the upper respiratory tract are discussed elsewhere [13].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_15

Noticeable blockage of the nose occurs in between 20% and 30% of pregnant woman and is termed pregnancy rhinitis (or rhinitis of pregnancy) [14, 15]. The definition of pregnancy rhinitis is that it is a condition in which there are symptoms affecting the nose in a pregnant woman, with a duration of at least 6 weeks, but further indications of infection within the respiratory tract or of an allergic response are absent, and there is complete resolution in less than 2 weeks after giving birth [12]. Sufferers from this condition describe chronic stuffiness in the nose, with the production of a watery or thick nasal discharge [11]. Because the nose is blocked, some women breathe through their mouths at night and sleep less well than usual. It is important to check there is no other more probable cause of the symptoms before making the diagnosis [16].

The pathogenic mechanism underlying pregnancy rhinitis is unknown. The hormones oestrogen ± progesterone have been thought by some to be implicated, but this explanation lacks confirmatory evidence [17]. One study concluded that being a smoker or having a hypersensitivity to house dust mite increases the risk of having pregnancy rhinitis [18], but sufferers do not have an increased prevalence of either asthma or seasonal allergic rhinitis [13].

The recognition of pregnancy rhinitis as a disorder in its own right, with attention to how it should be managed, is recent, albeit congestion has been known for a long time to occur in the nose during pregnancy. Recently, researchers have written about the high incidence of snoring in pregnant woman and commented on the adverse consequences this may entail, such as hypertension in the mother, pre-eclampsia, growth restriction or delay in utero and a low Apgar score [19]. Nasal congestion becomes more marked when an individual is lying flat, particularly where rhinitis is present [20]. Since pregnancy rhinitis can cause snoring, it possibly has graver consequences than were earlier appreciated [21].

Before air enters the lungs, it is heated, large particles are removed, and moisture is added by the nose. Nitric oxide released by the nose and sinuses also passes into the lungs, producing a vasodilatory response [22]. When an individual is forced to breathe through the mouth due to blockage in the nose, these physiological alterations to inhaled air do not occur. Indeed, patients with allergic rhinitis have a lower quality of life than asthmatic individuals, in all likelihood secondary to feeling excessively tired during the day, being thirsty, lacking the ability to concentrate and having headaches [23].

Oral breathing becomes more common in nasal congestion cases, resulting in drying out of the oral cavity. A lack of saliva predisposes a mouth-breather to dental cavity formation. Additionally, chronic nasal congestion may lead to sinusitis [21].

It is the alterations in physiology that occur in pregnant women that allow pregnancy rhinitis to develop, alongside more frequent nosebleeds and exacerbations in disorders affecting the nose and sinuses [24]. The circulating blood volume goes up in the first two trimesters of pregnancy, mainly accounted for by an increase in the volume of plasma. This extra fluid moves extravascularly in the final trimester. Oestrogen can act directly on the lining of the nose by stimulating cholinergic activity, thereby increasing blood flow and stimulating activity by the glands contained within the mucosa. If a disorder of the nose or sinuses is already present, it may be

exacerbated by these changes, although typically resolution occurs within 5 days of giving birth [25, 26].

The reported frequency of rhinitis and disorders of the nose and sinuses is between 20% and 40% in women of childbearing age. Ten to thirty per cent of these women reported an exacerbation of symptoms whilst pregnant [25]. The sinonasal disorders with which pregnant women are most likely to present for treatment are allergic rhinitis, sinusitis caused by bacterial infection and pregnancy rhinitis [27]. Rhinitis medicamentosa also occurs more frequently in pregnant woman, who tend to overuse intranasal decongestant sprays in the belief that they pose less danger to the unborn child than drugs taken orally [28].

15.2.1 Potential Foetal Impacts

The impacts of pregnancy rhinitis on the foetus appear to occur through alternations in maternal sleep quality. Nasal congestion becomes more marked when an individual is lying flat, particularly where rhinitis is present, as has been long recognized [20]. Impaired ability to breathe nasally tends to lead to oral breathing and snoring. In a cohort of 73,231 pregnant women, snoring occurred regularly in 9%, being found in association with elevated blood pressure, regardless of body mass index [29]. Research carried out by questionnaires sent to 502 women the day after they had given birth revealed that 23% of respondents had been regularly snoring the week before delivery [19]. Snoring had a significant association with being more likely to be hypertensive, suffering from pre-eclampsia, the foetus having growth restriction in utero and worse neonatal Apgar scoring [21].

15.3 Aetiology

Oedema in the nasal lining may be the result of decreased alpha-adrenergic vascular tone in the venous sinusoids, which results in blood gathering in the venous spaces. Plasma may also ooze out of the capillaries. Neither of these mechanisms currently appear to be under hormonal control [21].

15.3.1 Oestrogen

The main source for the idea that elevated oestrogen concentrations in pregnant women produce congestion of the nasal tissues is the research carried out by Toppozada et al. on nasal mucosal biopsies from pregnant women [30] and women on oral contraceptives [31]. Interestingly, research carried out at different points in the menstrual cycle found no evidence of cyclical mucosal alterations [32]. First-generation birth control pills, with high oestrogen content, had blockage of the nose as a side effect [21]. However, if oestrogen were the main cause of nasal blockage, this should occur in every pregnancy. Whilst there is evidence of increasing nasal

blockage as the pregnancy progresses [33], as shown by various measures, there are exceptions to this trend. One study found that, of 23 women studied, 8 did have worsening nasal blockage, but 9 women actually reported their nasal congestion improved over the time for which they were pregnant [34].

15.3.2 Placental Growth Hormone

Once the initial trimester has passed, instead of a periodic secretion of human growth factor (HGH), placental growth hormone variant (PGH) is released continuously at ever higher levels [35]. A study found that individuals suffering from pregnancy rhinitis had higher serological titres of PGH than individuals without the condition [36].

15.4 Risk Factors

A questionnaire-based study of pregnancy rhinitis found the condition to be more common if the woman is a smoker (odds ratio 1.7; 95% confidence interval 1.1–2.5) [18]. One explanation for this finding is that nasal irritation in combination with other physiological alterations leads to a congested nasal lining [21]. Stopping smoking is advisable for all pregnant women.

Toppozada et al. report that the appearances of nasal epithelium in pregnancy rhinitis matched those of allergic rhinitis, when viewed with the electron microscope [37]. When a group of 23 pregnant women were studied, the serological values for sICAM-1 (soluble intercellular adhesion molecule 1) did not significantly differ between women with pregnancy rhinitis and those without, nor did the level vary importantly over time [18].

15.5 Diagnosis

Some research investigating congestion of the nose in expectant mothers used very loose ways to define pregnancy rhinitis. It is usually assumed that the onset is as the first trimester is ending, and that resolution always occurs after the woman has given birth [30, 38]. A study that also enrolled non-pregnant control subjects found that complaints of nasal stuffiness only increased in the final trimester of pregnancy [39]. A different study with 23 pregnant subjects followed the women until 1 month after they had given birth and scored the level of nasal congestion every day, as well as recording nPEF (nasal peak expiratory flow) [33].

The sole symptom of sinusitis in some pregnant women is a blocked nose [37]. It can be difficult to diagnose sinusitis at the best of times, even without the complication of pregnancy. A blocked nose does not rule the diagnosis in or out. It has been suggested that the presence of pus in the middle meatus, smelling a foul odour in the nose, a pus-filled discharge especially on one side and pain confined

to one side are all clear pointers to a diagnosis of sinusitis [40]. However, the situation may be more complex, notably so when cases first consult their general practitioner [41].

Where suspected disease in the nose and sinuses has not responded to conservative therapy, a radiological assessment can be very cautiously sought, but should not be considered in the initial trimester. The period of foetal development occurring between 10 and 17 weeks post conception is an especially dangerous time for the developing nervous system to be exposed to radiation, and thus X-rays should be avoided at this stage [42]. The consensus is that the foetus should not be exposed to any more than 5 rad of ionising radiation for the whole period in utero. No diagnostic radiological procedure supplies more than 5 rad exposure [43]. Where antimicrobial therapy has not improved sinusitis or it is worsening, imaging may indeed be required to ensure intracranial or orbital extension is not overlooked. Magnetic resonance imaging of the paranasal sinuses does not entail exposure to ionising radiation, but comes with certain caveats: it is better to use a contrast agent, which can be teratogenic; it is a harder study to perform; and it has limited value in surgical planning. Thus, it is necessary in such cases to offer CT minus contrast, at the same time providing information about the potential for harm to the foetus, including the fact that quantifying the risk is at present problematic [1].

15.6 Treatment

Pregnancy rhinitis usually resolves spontaneously, without intervention. In any case, the benefit from intervening is minimal [13].

Every pregnant female should be advised that pregnancy rhinitis exists [29].

Physiological measures may improve nasal blockage, such as raising the head of the bed. Patients may have forgotten to try this simple expedient. The optimal angle has been reported as 30° [20] or 45° [44].

Performing physical exercise is known to promote decongestion of the nasal lining [45]. Moreover, it may assist with disturbed sleep resulting from a blocked nose. The naturally occurring fatigue and sense of well-being that accompany exercise may also make the woman sleep better.

15.6.1 Nasal Saline Irrigation

Five milligrams of sodium chloride dissolved in 0.5 L water, in the opinion of the authors, assists in cases of pregnancy rhinitis, just as with rhinitis from other causes [21].

The US FDA have published pregnancy risk categories which allow doctors to make informed prescribing choices when treating pregnant patients. Currently, no drug used for sinonasal disorders falls within Category A, due to the non-existence of high-quality trials in human beings. However, defensible practice allows the use of Category B products, where animal studies have not shown a lack of safety [46].

Products in Categories C and D, where a safety concern has been shown in either humans or animals, must only be used rarely [47].

Oral decongestants should not be prescribed during the first trimester because they may raise the risk of gastroschisis in the foetus [48]. They may additionally exacerbate hypertension [49]. In non-hypertensive women, pseudoephedrine appears safe in the mid and final trimester [13].

Budesonide is an agent in Category B and is the best understood from a safety viewpoint [50]. Sprays developed recently typically do not enter the circulation in appreciable amounts and thus may have an acceptable safety profile, but definite positive evidential support for the safe use of these agents in pregnancy does not yet exist. The evidence covers the usual dosage range for budesonide, 50 μg per nostril o.d. or b.d. being normally adequate to control chronic rhinosinusitis in pregnancy and remain safe [9].

Montelukast currently falls in Category B, and there is a registry of individuals who have been exposed to the agent when pregnant. Although montelukast is known to be passed into breast milk, data are lacking on what harms might occur to babies being breastfed. It is reasoned that the drug undergoes extensive metabolism and is largely protein-bound, which may reduce harmful effects. One per cent of the dose administered enters breast milk. However, the benefit from breastfeeding outweighs any risks from the agent. A further piece of advice for nursing mothers is to feed the infant before taking the dose, so as to reduce exposure via breast milk to a minimum. 5-Lipoxygenase inhibitors are contraindicated both in pregnancy and during lactation [51].

15.7 Do Treatments Carry Risks in Pregnancy?

All steroid treatments taken orally and decongestants by mouth are within category C and are contraindicated in the initial trimester [52]. Whilst the nasal sprays do not get absorbed into the general circulation to an appreciable extent and thus are less risky for a pregnancy, they are each within category C, with the only exception being budesonide. Skin prick testing for allergies is not permissible during pregnancy, since there is a possibility of an anaphylactic reaction occurring. Immunotherapy that commenced before the onset of pregnancy may carry on, provided the maintenance dose is adjusted downwards [53].

Oral steroids are anticipated to raise the risk of cleft lip and/or cleft palate [54] and raise the probability of pre-eclampsia and may result in prematurity or being underweight at delivery [55, 56]. However, leaving asthma untreated entails more risk for the mother than steroids entail for the foetus. For chronic rhinosinusitis, the advantages do not so evidently outweigh the risks, and thus clinicians must use their discretion. The riskiest period from the point of view of causing birth defects is the initial trimester. Steroids may produce hyperglycaemia and set off or worsen diabetes mellitus, which entails more danger to both mother and foetus. It is advised that patients being prescribed steroids, especially over a prolonged period, should be

first tested for diabetes. According to the view of the American Academy of Pediatrics, breastfeeding is not a contraindication to oral steroid therapy [9].

Aspirin falls into category D and its use is contraindicated. Both aspirin and the NSAIDs in general are associated with untenable risks, in particular with too early closure of the ductus arteriosus. Aspirin has an association with restricted foetal growth and perinatal death. Patients with previous immunotherapy for aspirin and on maintenance treatment need to stop aspirin if they plan to become pregnant or immediately if a pregnancy becomes known [9].

Decongestants taken by mouth may raise the risk of gastroschisis in the foetus and may additionally exacerbate hypertension [49].

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Paediatric Rhinitis and Rhinosinusitis

16

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16.1 Introduction

Rhinitis may be defined as an inflammatory condition affecting the upper airways in which rhinorrhoea, nasal congestion or sneezing (or any combination thereof) has been present a minimum of 2 days in a row and lasts for at least 1 h on the majority of those days [1, 2]. The Allergic Rhinitis and Its Impact on Asthma (ARIA) guideline distinguishes two categories of rhinitis: allergic rhinitis (AR) and non-allergic rhinitis (NAR). The differentiating feature between these conditions is whether allergic sensitisation has taken place (i.e. AR) or not (NAR). The pathophysiology of AR depends on IgE, and it is usual for ocular pruritus, indicating conjunctivitis, to be present as an additional presenting feature. NAR may be caused by several different pathological processes, such as infections, endocrine disorders and occupational exposure, or simply idiopathic (also termed as vasomotor rhinitis) [2].

Whilst rhinitis is rarely thought of as a fatal disorder, it does impact significantly on the quality of life of rhinitis sufferers and their carers, as well as being associated with an economic burden for society as a whole. Rhinitis often co-exists with other disorders, such as otitis media with effusion, hypertrophied adenoids and asthma, and this is an important point to bear in mind when treating children with rhinitis. Drug treatment options are few for paediatric cases under 2 years old [1]. Two

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_16

studies which followed up a birth cohort found that rhinitis in childhood became more and more frequent as the children grew from infancy into childhood and adolescence [3, 4].

Rhinitis frequently occurs in children and adolescents [1, 2]. It is commonplace to dismiss the significant morbidity associated with the condition by viewing rhinitis as a self-limited coryzal illness. However, sternutation, pruritus, watery nasal discharge and nasal congestion are distressing for patients. The presentation in childhood and adolescence may also be atypical, with coughing or snoring. Rhinitis has an adverse effect on biopsychosocial well-being [5, 6]. Academic achievement may be negatively impacted directly by symptoms and indirectly through somnolence resulting from disturbed sleep or by sedation occurring as a side effect of histamine blockade [4].

16.2 Classification of Rhinitis

Rhinitis is an inflammatory condition affecting the nasal mucosa, with two or more of the following symptoms needed to make the diagnosis: sneezing, pruritus, nasal congestion and nasal discharge. Rhinitis may present in a variety of forms, with some overlapping features. The most usual persistent type of persistent rhinitis is allergic rhinitis (AR), where the symptoms are triggered by contact with a substance which has previously produced sensitisation, i.e. allergy. It is the fact that sensitisation has occurred that forms the basis for assigning symptoms to AR [2]. Rhinitis may be subdivided as follows [7]:

1. AR: Sensitisation to a particular antigen precedes the development of rhinitis symptoms.
2. Infectious rhinitis: An infective agent is involved.
3. Non-allergic, non-infectious rhinitis: The trigger may be endocrine (hypothyroidism), a side effect of medication (e.g. beta-blockade, NSAIDs), neurological, gastroesophageal reflux or of unknown cause.

AR has both a periodic (seasonal) and persistent (year-round) form, depending on whether the allergen exists throughout the year or not. This distinction does not always exist, and thus the Allergic Rhinitis and Its Impact on Asthma (ARIA) group [2] has now dispensed with this classification. Instead, ARIA guidelines separate AR into intermittent or chronic forms and, with severity of mild or moderate to severe, are based on how sufferers' lives are affected [2].

16.3 Epidemiology

Globally, rhinitis is a very frequent disorder in children. The third-phase trials in the International Study of Asthma and Allergies in Childhood (ISAAC) (dating from 1999 to 2004) found that the mean rate of occurrence was 8.5% (1.8–20.4%) in

cases between the ages of 6 and 7 and 14.6% (1.4–33.3%) in cases between the age of 13 and 14 [8]. It was noted that rhinoconjunctivitis had risen in frequency across the globe when results were compared with those of the first phase, carried out using the same technique in the period 1991 to 1998, but the differences between study centres were considerable [9].

A variety of studies have examined the course rhinitis takes in children. The Isle of Wight birth cohort, consisting of 1456 children born in 1989, discovered the prevalence in unsensitised children to be 2.8% in 4-year-olds and 11.8% in 18-year-olds, whilst in children who had undergone sensitisation, the corresponding figures for ages 4 and 18 were 3.4% and 27.3% [4]. Male adolescents were more likely to have allergic rhinitis, whereas female adolescents were more prone to non-allergic rhinitis. The MAS study participants (all aged up to 13 years) had a comparable prevalence of rhinitis [10]. Young children who suffer from allergic-type rhinitis have a greater risk of eventually becoming asthmatic, either as children [11] or adults [12], but this is not the case with non-allergic rhinitis.

16.4 Allergic Rhinitis

Allergic rhinitis (AR) has a prevalence of 30% in adulthood and 40% in childhood [13]. AR in childhood more commonly affects males than females, with symptoms generally present by the age of 20 years [14]. Year-round symptoms in a child usually persist when the child becomes an adult, but where symptoms are confined to a particular season, there is a 20% likelihood that AR will no longer be present when the child enters young adulthood [15].

16.4.1 Risk Factors

AR is associated with the following risk factors: living in an area of high pollution, being non-Caucasian and being from a more affluent background. A number of other associations with increased risk have also been identified, such as being exposed to allergenic triggers as a young child within buildings, having a mother who smokes and early weaning or transfer to bottle feeding whilst still an infant [14]. Sixty per cent of sufferers have a family member with AR, pointing to a genetic basis [15]. Some other disorders also increase the risk, notably allergic eczema, dermatitis, asthma and other allergic conditions. Around 20% of sufferers from AR have co-morbid asthma [14].

16.4.2 Signs and Symptoms

Patients suffering from AR may provide a simple account of their problem, or it may appear complicated. Diagnosing AR is straightforward if symptoms follow a seasonal pattern or are linked to the arrival of a pet animal. A young child with AR

may present in many different ways, with family members not realising the child feels stuffy, but may observe that the nose seems to be blocked for prolonged periods. Young patients whose symptoms appear attributable to seasonal pollen variation may actually be sensitised to dander, the shedding of which is itself seasonal, being shed in spring and building up again in the autumn. An older child with AR may wrongly seem to have only mild symptoms, since the chronic timescale involved has allowed the child to adjust to being unwell. AR in a child presents with the following signs or symptoms [16]:

- Nasal discharge, blocked nose, postnasal drip.
- Pallor of the turbinates within the nose. Rhinorrhoea (watery) may also be present.
- Repeatedly sneezing.
- Palatal, nasal, ocular or otic pruritus.
- Snoring.
- Pharyngitis that keeps recurring.
- Needing to clear the throat all the time and coughing.
- Headache.
- Diagnosis.

To assess a child fully for AR, the head, eyes, ears, nose and throat all need to be examined. Signs that may be expected include the following:

- On the head: periorbital hyperpigmentation (dark, swollen lower eyelids), infraorbital fold (Dennie-Morgan line), allergic salute (gesture of wiping nose repeatedly) with formation of a crease in the nose between the lower and upper two thirds.
- Eyes: the palpebral conjunctivae become reddened, and the papillae may become hypertrophied; the conjunctivae become chemotic, typically with a watery discharge; it is possible for cataracts to develop if pruritus is severe and results in excessive rubbing by the patient.
- The middle ear may be persistently infected and an effusion may be present.
- Nasal findings: the conchae are bigger than usual, and mucosal appearances alter due to swelling, becoming faintly blue. Rhinorrhoea (typically whitish, but occasionally yellow or green) is present. Dried blood may be found, from rubbing the nose hard enough to cause injury. It is rare for polyps to be present, but if rhinoscopic examination reveals their presence in a child, cystic fibrosis must be excluded as the cause.
- Pharynx. The mesial incisors may be a different colour and the palate unusually highly arched, and malocclusion may occur. All these changes are related to breathing for prolonged periods via the mouth. The posterior pharynx may have a cobblestone-like appearance because of persistent blockage of the nose and postnasal drip.

16.4.3 Testing

Where a clear history is obtainable that is consistent with AR, laboratory confirmation is unnecessary. However, if the history is unclear, some investigations may be of benefit, amongst which are the following [16]:

- Cutaneous prick test. This has both high sensitivity and specificity for airborne antigens.
- Specific IgE to known or suspected allergens.
- Total circulating IgE. Whilst raised IgE may hint at the diagnosis, it lacks the sensitivity of cutaneous prick tests.
- Nasal smear.
- Cutaneous allergy tests are of benefit in the identification of allergenic triggers. Both skin pricking and intradermal methods may be used.
- Consideration should be given to performing spirometric studies, since up to 70% of asthmatic children have co-morbid AR.
- Rhinoscopic examination may aid in differentiating between blockage and infection as the cause of rhinitis and to assess any polyps within the nose [16].

16.4.4 Treatment

1. Pharmacological/medical

   There are two principal types of agent useful to treat AR: histamine blockers and steroid inhalers. A number of other agents are sometimes employed, too. The list encompasses decongestants, anticholinergic agents, mast cell stabilisers and leukotriene antagonists.

   (a) *Antihistamines*

   Second-generation antihistamines do not penetrate the blood-brain barrier and have lesser sedation (e.g. cetirizine, acrivastine) or lack sedation altogether (fexofenadine, loratadine, desloratadine) [17, 18].

   (b) *Intranasal antihistamines*

   Amongst histamine blockers that are applied intranasally, there is azelastine, which comes as a metered-dose intranasal spray. It is only available on prescription. The agent has rapid onset and is as efficacious in reducing nose-related symptoms of AR as systemic antihistamines by mouth are [19]. Azelastine can lessen nasal blockage. As the drug is absorbed through the nasal lining, it has some sedative action and may cause a bitter taste [20]. FDA approval has been granted in paediatric cases of AR over the age of 5 years [19].

   (c) *Decongestants*

   Decongestants should only be prescribed in paediatric cases where there is a substantial degree of nasal blockage and other treatments have failed [13].

(d) *Anticholinergic agents*

Ipratropium bromide is an anticholinergic agent employed intranasally to block cholinergic transmission and thus reduce the secretion of mucus in the nasal lining [17]. The most frequent side effects are headache, nosebleeds and dry nose. Care must be taken in prescribing ipratropium bromide if a patient has angle-closure glaucoma, obstruction of the bladder outlet or prostatic hypertrophy. There are nasal solutions available at strengths of 0.03% and 0.06%. The indication is to relieve symptoms of nasal discharge secondary to AR or NAR (non-allergic rhinitis) in patients aged over 5 years [21]. Dosage range is two sprays to both nostrils and may be b.d.s., t.d.s. or q.d.s.

(e) *Mast cell stabilisers*

Mast cell stabilisation prevents mast cells that have previously been sensitised from releasing their granules, both preformed and freshly synthesised [17]. There are no known interactions with other medications for cromolyn sodium. It is an over-the-counter medication in the form of a metered-dose intranasal spray, licenced in those aged above 2 years of age [22]. The side effects involve sneezing, irritation, stinging and burning to the nasal lining [23].

(f) *Intranasal corticosteroids*

Steroids applied intranasally work by inhibiting inflammatory responses and thus reducing the symptoms of AR [17]. They prevent the recruitment of polymorphonuclear leukocytes and fibroblasts and reduce the leakiness of the capillaries, whilst also acting to make the membranes of lysosomes more stable. These actions result in reduced or absent inflammatory responses [17, 23]. This class encompasses beclomethasone, triamcinolone, flunisolide and budesonide (licenced in patients at least 6 years old), fluticasone (licenced in patients at least 4 years old) and mometasone (licenced in patients at least 2 years old). Whilst all such agents have acceptable levels of efficacy, the second-generation corticosteroids (mometasone and fluticasone) benefit from being less bioavailable and hence possibly being safer in long-term use [24].

(g) *Antileukotriene antagonists*

Antileukotriene antagonists (including montelukast) are selective leukotriene receptor antagonists, acting through inhibition of the cysteinyl leukotriene CysLT1 receptor [13, 14]. The evidence base supporting directly the use of such agents in young children suffering from AR is slender, but data obtained in adolescents and adult sufferers from AR appear to suggest benefit. Research was undertaken involving 1302 cases of hay fever aged 15–81 years old. Treatment allocation occurred through randomisation. The groups took one of montelukast 10 mg, loratadine 10 mg (active control), or placebo. The treatment duration was 2 weeks. When montelukast was compared with the inactive control, there were significant improvements in both nocturnal and diurnal symptom scores [25].

2. Allergen-specific immunotherapy: This is the sole treatment that is truly curative. The form depends on the allergen responsible for the patient's symptoms [16]. SIT (allergen-specific immunotherapy) entails treating disorders of an allergic aetiology occurring through IgE. Recipients of the therapy must be at least 6 years old [26]. Therapy may be given subcutaneously or sublingually [7].
3. Saline irrigation of the nose: This achieves efficacy in around 50% of cases suffering from AR [16].
4. Exclusion of the allergenic trigger, where feasible [16].

16.5 Paediatric Rhinosinusitis

Rhinosinusitis by definition involves mucosal inflammation within the nose and paranasal sinuses. Chronic rhinosinusitis (CRS) frequently occurs in children. Diagnosing and treating CRS is not straightforward, since it is a persistent condition which shares overlapping symptomatology with AR and adenoidal hypertrophy [27].

Despite being rarer than acute rhinosinusitis in children, CRS is increasing in frequency. Children often experience a reduction in their quality of life as well as disruption to everyday activities. The characteristic features are symptoms attributable to a sinus disorder that persist beyond 3 months, in spite of pharmacological intervention. There is a complex pathophysiology, involving initial viral infection and secondary bacterial superinfection, inflamed mucosae and an atopic diathesis [27].

"Rhinosinusitis" is more apt to describe the disorder than "sinusitis", given the virtually invariable pattern of sinusitis occurring in conjunction with, or following, rhinitis. Classification depends on the length of symptoms, with "acute" rhinosinusitis lasting a month or less, "subacute" lasting 1 to 3 months and "chronic" persisting beyond the 3-month mark. The diagnosis of acute bacterial rhinosinusitis (ABRS) in children depends on the presence of the following: symptoms of the upper respiratory tract (coughing, rhinorrhoea) of greater than 10 days' duration; worsening of symptomatology despite previous improvement (pyrexia, increasingly severe coughing, purulent nasal discharge); or significant pyrexia or purulent rhinorrhoea occurring for longer than 3 days in a row and in conjunction with a sore face or headache [28]. ABRS is often secondary to infection by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Approaching 5–10% of paediatric cases of upper respiratory tract infection by viruses go on to become ABRS [29, 30]. Of these cases of ABRS, some then evolve into CRS. ABRS and rhinosinusitis secondary to viral infection share many presenting features, both clinical and imaging-related, which makes it complex to distinguish between the two conditions [27].

The pathophysiology of CRS is more complex than that of ABRS, involving, as it does, the interaction of numerous influences, both inherited and environmental. Untreated CRS has a more detrimental effect on patients' quality of life than many other chronic disorders of the respiratory or musculoskeletal system [31].

The principal therapeutic approach in paediatric cases of CRS is pharmacotherapy aiming to treat microbial infection and damp down the inflammatory reaction in the nose and paranasal sinuses. Operative techniques, e.g. sinus puncture and lavage, adenoid removal, balloon sinuplasty, endoscopic sinus surgery, open surgery and debulking of the turbinates, are only utilised when pharmacotherapeutic options have been exhausted [32]. Surgical interventions share the objectives of preventing the build-up of bacteria and improving the ventilation and drainage of the sinuses [33].

16.5.1 Microbiology

Some 5–10% of paediatric cases involving infection of the upper respiratory tract (URTI) involve ABRS [30, 34]. A report that appeared recently in the *Pediatric Infectious Disease Journal* [35] noted that a viral pathogen was isolated in 63% of cases at initial presentation for a URTI and that the presence of rhinovirus correlated strongly with the chance of developing ABRS ($p = 0.01$). In 99% of cases, microbiological sampling at this appointment grew a bacterial culture. Fifty-six were polymicrobial, 20% grew *M. catarrhalis*, and, in 10% of the sample, *S. pneumoniae* were isolated. Other pathogens identified at a lower frequency were streptococci of groups A and C, peptostreptococci, *Eikenella corrodens* and organisms of the *Moraxella* genus [36, 37].

16.5.2 Predisposing and Co-morbid Conditions

16.5.2.1 Genetic

It has been shown that CRS is strongly heritable, on the basis of familial association studies. The heritability is from immediate or secondary blood relatives. A recently published study conducted by Orb et al. examined CRS heritability in 496 cases and observed that genetic factors predispose to the development of the disease. Having a relative with CRS increased the risk by 57.5-fold. In children, the risk in first cousins of CRS cases is elevated nine-fold from background, whereas in second cousins, it is 2.9 times higher [38].

16.5.2.2 Allergy

AR both contributes to and co-exists with CRS in children [33, 38]. A study that examined 4044 paediatric CRS cases in retrospect deduced that AR occurs more frequently in this group than all the other co-existing pathologies (cystic fibrosis, primary ciliary dyskinesia and other immunological conditions) combined. Nonetheless, comparison of the frequency of AR in general with the frequency in CRS sufferers showed no difference. This implies that testing for hypersensitivity to airborne allergens is vital in working up a paediatric case of CRS [29].

16.5.2.3 Asthma

Just as AR co-exists with CRS, so does asthma. Both clinical experience and pathophysiological considerations point to overlapping demographics. The histological appearances of the nasal epithelium in AR sufferers and the mucosa of the bronchi in asthma sufferers are similar—both feature mast cells and eosinophilic infiltration [30]. Moreover, individuals with rhinitis who encounter allergic triggers undergo infiltration of both the nasal lining and the bronchial epithelium by eosinophils. Indeed, it has been demonstrated on repeated occasions that satisfactory management of CRS leads to reduced asthma symptomatology and necessitates fewer accident and emergency attendances in children who have both disorders [27].

16.5.3 Diagnosis

The Infectious Diseases Society of America (IDSA) proposes in its guidelines that the following criteria allow a diagnosis of ABRS to be made:

- Symptoms of an URTI persisting longer than 10 days and not improving.
- Indications of a severe illness, such as markedly raised pyrexia (exceeding 39 °C), facial tenderness or pus-filled rhinorrhoea, are present for at least 3 or 4 days.
- A secondary deterioration in condition (i.e. “double sickening”) in the clinical presentation of a child with an otherwise classical URTI lasting 5 or 6 days, which appeared to be getting better. Pyrexia, headache or copious rhinorrhoea may now be present.

Plain X-rays lack both sensitivity and specificity to allow diagnosis of sinusitis and thus are generally not required for diagnosis or monitoring in acute rhinosinusitis or CRS. CT (computed tomography) is a superior modality, with coronal and axial sections being required. CT imaging of the sinuses limited to the coronal plane reveals the degree of patency of the ostiomeatal unit and reveals the anatomical configuration of the sinuses. Contrast agent is typically only employed if there is clinical suspicion of an abscess within the orbit or intracranially. Rim enhancement permits more confident assessment of a potential abscess and planning for operative intervention if required. The finding of a radiological triad of air-fluid level, partial or total opacification and membranous thickening of 4–6 mm points to sinusitis as the diagnosis. Whilst radiological assessment is not routinely necessary to diagnose sinusitis, if CT images lack evidence of sinusitis, the diagnosis can be confidently excluded [36]. Since 45% of unselected children have abnormal CT scan, probably related to frequent viral colds, they cannot be used as an isolated diagnostic measure.

16.5.4 Treatment

16.5.4.1 Acute Rhinosinusitis

Amoxicillin at a high dosage (90 mg/kg/day) is the treatment of choice in sinusitis since it possesses efficacy against the pathogenic bacteria responsible for sinusitis. Infections due to *H. influenzae* appear to be on the rise, and more strains now produce β-lactamase; hence it is better to use clavulanic acid in conjunction with amoxicillin. A dose of 90 mg/kg/day is acceptable to cover *S. pneumoniae* infections, which are resistant to penicillin [39]. Cephalosporin antibiotics (cefpodoxime, cefdinir or cefuroxime) may also be used, although they possess less activity against *S. pneumoniae* than co-amoxiclav. In paediatric cases where co-amoxiclav or treatment with a second- or third-generation cephalosporin is unsuccessful, either cefixime or cefdinir can be combined with linezolid, in place of intravenous antibiotics. If there are contraindications to the use of beta-lactam-containing agents, fluoroquinolones with action against respiratory pathogens (levofloxacin or moxifloxacin) can be prescribed, as can doxycycline. When choosing an antimicrobial, it is important to consider the pattern of susceptibility in the particular region [27].

16.5.4.2 Chronic Rhinosinusitis (CRS)

Children with CRS who have co-morbid AR gain benefit from avoiding exposure to the allergen, histamine blockers and intranasal steroid therapy. SIT is likely underutilised despite its potential to alter the prognosis of the disorder by alleviating symptomatology and decreasing reliance on medication [40]. Evidence proving that SIT is of benefit does exist for AR, but this is not the case for CRS [27].

16.5.5 Surgery

Operative techniques are not the preferred treatment modality in CRS and are reserved for when complications exist and pharmacological therapy has failed or if an underlying anatomical anomaly is thought to be present [39, 41].

The adenoids harbour pathogenic bacteria in paediatric cases of CRS, whatever their actual size; hence adenoidectomy is associated with an improvement in prognosis [30, 34]. In cases below the age of 6 years, adenoid removal has a high level of efficacy as a first-line operative treatment. Nonetheless, for cases aged 6–12 years, adenoidectomy declines in effectiveness. In older children, there is no consensus on the efficacy of adenoidectomy. Tonsillectomy alone (i.e. not adenotonsillectomy) is not valuable in treating paediatric CRS [35].

Surgical interventions of all types (adenoid removal, sinus puncture and lavage, endoscopic sinus surgery, turbinate reductions and open operations) are only used where pharmacotherapy fails [37].

16.6 Non-allergic Rhinitis (NAR)

It has often been the case that NAR is only considered as a diagnosis where sensitisation has demonstrably not previously occurred. The tendency has been to wrongly attribute symptoms to local allergic rhinitis or to fail to note rhinitis of mixed causes. Nasal smears are well-suited to everyday paediatric clinical practice and have the potential to improve the diagnosis of NAR whilst also supplying vital hints on the epidemiology of the condition and on how it is best managed [42].

16.6.1 Definition

At present, NAR is usually considered when a case has appropriate clinical features and AR can be discounted. NAR is a persistent disorder affecting the nasal lining, with characteristic nasal blockage and discharge, but negative cutaneous prick tests and non-raised sIgE for allergic triggers in the environment [43].

Whilst NAR has usually been thought to be more frequent in adults than children, it is likely to be fairly prevalent in children, too. It is to be regretted that the precise prevalence rates and degree of morbidity in the paediatric range is unknown. One reason for this gap in our knowledge is that children rarely undergo allergic challenge testing [44]. Compounding this problem is the lumping of several different clinical entities together under the umbrella term "NAR". This has led to confusion in the literature about the epidemiology of the disorder, fed by inconsistency in terminology and ways of classifying the various disorders. Even now, classifying NAR still depends on whether particular conditions co-exist and what triggered the latest episode. The pathological features also need to be considered. In the absence of a clear classification, the majority of cases of NAR have been categorised as essential or vasomotor in origin [45].

16.6.2 Classification

According to the Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis, edited by the European Academy of Allergy and Clinical Immunology (EAACI) [46], there is recognition of the following subtypes of NAR: (1) non-allergic rhinitis with eosinophilia syndrome (NARES); (2) endocrine-related rhinitis (which occurs in pregnancy, acromegaly and hypothyroidism or is linked to the menstrual cycle); (3) rhinitis of the elderly; (4) gustatory rhinitis (hot and spicy foodstuffs and drinking alcoholic beverages, amongst others); (5) atrophic rhinitis (primary or secondary to sinus surgery, autoimmune and/or immune-mediated diseases); (6) cold air-induced rhinitis (precipitated by cold and/or windy weather); (7) medication-related rhinitis (nasal decongestants, aka "rhinitis medicamentosa", aspirin, oral

alpha- and beta-blockers, phosphodiesterase inhibitors, calcium channel blockers and neuroleptics, amongst others); (8) occupational non-allergic rhinitis (irritants, corrosive substances); and (9) idiopathic rhinitis ("vasomotor rhinitis").

The NAR Consensus Panel of the World Allergy Organization (WAO) has produced a not dissimilar scheme to classify NAR. This scheme does not allow for the presence of either nasal anatomical/mechanical anomalies or CRS. Disorders that produce systemic consequences (endocrine or metabolic diseases, autoimmune conditions and various other disorders) as well as producing symptoms corresponding to NAR are under a different heading. This leaves eight categories of NAR: (1) medication-related rhinitis, (2) gustatory rhinitis, (3) endocrine rhinitis (including responses to naturally occurring female hormones: in essence, pregnancy rhinitis), (4) NARES, (5) rhinitis of old age, (6) atrophic rhinitis, (7) leakage of cerebrospinal fluid and (8) non-allergic rhinopathy (encompassing vasomotor rhinitis and rhinitis triggered by extremes of weather) [47].

16.6.3 Diagnosis

It remains the case that diagnosing NAR in paediatric cases hinges for the most part on being able to exclude AR. This stems either from the unfeasibility of performing certain diagnostic tests, such as specific nasal provocation testing, rhinomanometry or acoustic rhinometry, in normal paediatric practice, or from the tests being insufficiently sensitive or not fully standard, such as nasal-specific IgE or basophil activation testing. As indicated earlier, nasal smears have great promise in this group of patients and permit an inflammatory characterisation of the various subtypes. Some work has already been undertaken on the use of cytological techniques in children [42].

16.6.4 Treatment

For the most part, therapy for NAR consists of antihistamines, with or without intranasal corticosteroids. Other agents are indicated for particular problems, e.g. if nasal discharge is the sole or most distressing symptom of NAR (as is typical of vasomotor rhinitis), a topical anticholinergic agent, ipratropium bromide, may be useful. There is no direct evidence for the use of ipratropium bromide spray in children with NAR, but a study which examined its use in paediatric patients with nasal discharge resulting from allergic reactions or coryza did conclude that it was straightforward to use and tolerably safe and possessed efficacy, even in patients aged only 2 years old [48, 49]. In paediatric patients generally, nasal lavage is an initial intervention in rhinitis of whatever cause and appears beneficial in NAR. Research has shown nasal lavage lessens the severity of nasal symptoms, leading to less postnasal drainage, blockage of the nose or sneezing. It appears that nasal washing assists with mucociliary drainage, which expels allergenic substances, biofilms and pro-inflammatory molecules from the nose [50, 51].

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Have Technical Advances Improved CRS Outcomes?

17

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17.1 Introduction

Yes, undoubtedly, some of these tools have made endoscopic sinus surgery more effective. One should not rely exclusively on the technical privileges that new instruments, equipment, and utensils offer simply because the most important thing to perform successful surgery is not the "weapon," regardless of how splendid it is. The battle in general, particularly in surgery, never is won by splendid weapons but owing to a brilliant mind and skills of the fighter.

17.2 Computed Tomography (CT)

Prior to CT scanning, what we were able to see by radiological techniques was usually Waters' projection (Fig. 17.1), also named as "occipitomental view" (a radiographic view, where an X-ray beam is angled at 37° to the orbitomeatal line), mostly as to depict the maxillary and sinus, not ethmoid sinuses and particularly not sphenoid sinus. In particular cases, but not routinely, tomography of the sinuses was used. Both Waters' projection and tomography of the sinuses (Fig. 17.2) were just approximate, without any precise demonstration of the bony structures of the sinuses.

The information given by computed tomography (CT) of the paranasal sinuses needs to be interpreted according to the patient's history and examination. Incidental mucosal changes are found in a third of asymptomatic adults and 45% of children [1].

Anatomical variations found in the paranasal sinuses are no more common in symptomatic patients, making it unlikely that these either initiate or sustain paranasal sinus disease.

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_17

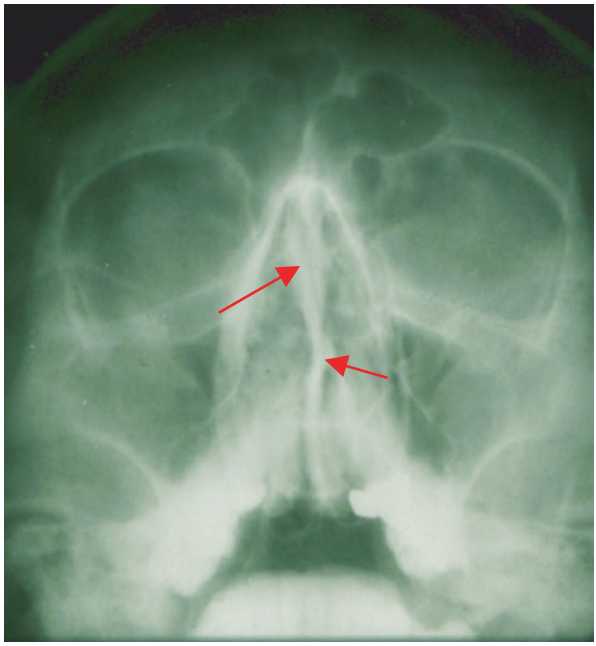

Fig. 17.1 Radiologic Waters' projection. An experienced eye can recognize in this picture only that something was going on with the form of the nasal septum (red arrows) and a kind of shroud over both maxillary sinuses

CT provides a roadmap for the surgeon and is vital in the diagnosis of atypical sinus infections, malignancy, and CRS (chronic rhinosinusitis) complications. ENT surgeons need to communicate with radiological colleagues, giving the details of the presentation to obtain maximum benefit from the scan. So the development of minimally invasive sinus surgery, particularly in terms of the functional endonasal endoscopic sinus surgery (FESS) techniques, was enabled owing to the advances in radiological imaging like axial, coronal, and sagittal projections in computed tomography (CT) scanning, as well as the nuclear magnetic resonance (NMR) scanning. We are now able to see many anatomical details without entering into the skull and sinuses; everything is perfectly visible! Rhinologists should not rely exclusively on the radiological findings; they should be able to "read" the CT or NMR scans by themselves. During over 30 years of working with CT scans of the paranasal sinuses, radiologists have failed to mention sinus septi nasi nor the defect of the lateral nasal wall next to the natural ostium of the maxillary sinus. Pneumatized crista galli with obvious content inside has never been described.

17.3 Navigation Systems

The navigation system is a relatively new tool which appeared during the last decade of the twentieth century [2]. Later on, more authors started to report their results and experiences with navigation systems in FESS [3–5, 11]. Nowadays, navigation systems (Fig. 17.3) are widely used.

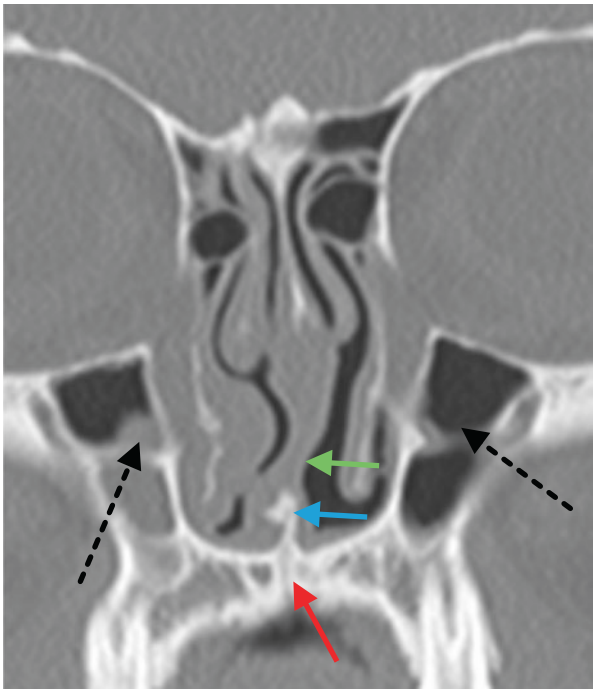

Fig. 17.2 A coronal CT scan showing the following signs: suspected submucosal cleft palate (red arrow—the palatal processes of the right and left maxilla are not in contact), and intermaxillary bone is distorted (blue arrow): it usually has the shape of the capital letter "Y" and usually is "inserted" between the palatal processes of both maxillas. This intermaxillary bone is asymmetric; the right "ala" of the letter "Y" is positioned very low, whereas the left ala is sticking in an upright position. Because of that, the inferior border of the anterior nasal septum had the opportunity to slide out of the naturally presumed "holder" (made by two symmetric alas of the letter "Y"). It skipped out to the right nasal cavity from the bolster and thus formed so-called septal anterior crest, while on the opposite left side, a very typical groove (green arrow) appeared as a consequence of septal sliding out. The groove is the "trademark" of the famous type 6 septal deformity, very frequently connected to the cleft palate. One can see also that something is going on in both maxillary sinuses; they even seem to be partially unusually septated, i.e., divided in the superior and inferior "floor," mostly in their posterior part (black arrows). The right maxillary sinus seems to have some content of discharge or even polypous tissue, particularly in the "lower floor." The ostiomeatal complex looks unhealthy bilaterally as does the ethmoid sinus, while the crista galli looks unusual. Such features would not have been seen and recognized in previous radiological images like Waters' and tomography images. This is the real advantage of a correctly performed CT scanning of the paranasal sinuses. CT scanning has changed the complete concept of diagnosis, treatment, and surgical approaches to the paranasal sinuses

As to possible advantages of such systems, I can say that most of the standard procedures of the endonasal endoscopic sinus surgery can be performed without the help of navigation. Still, sporadic pitfalls with this technique can result in serious complications, particularly when dealing with anterior skull base, pituitary gland surgery, CSF leak connected to the skull base tumors, etc. Under the assistance of a navigation system, these can be avoided.

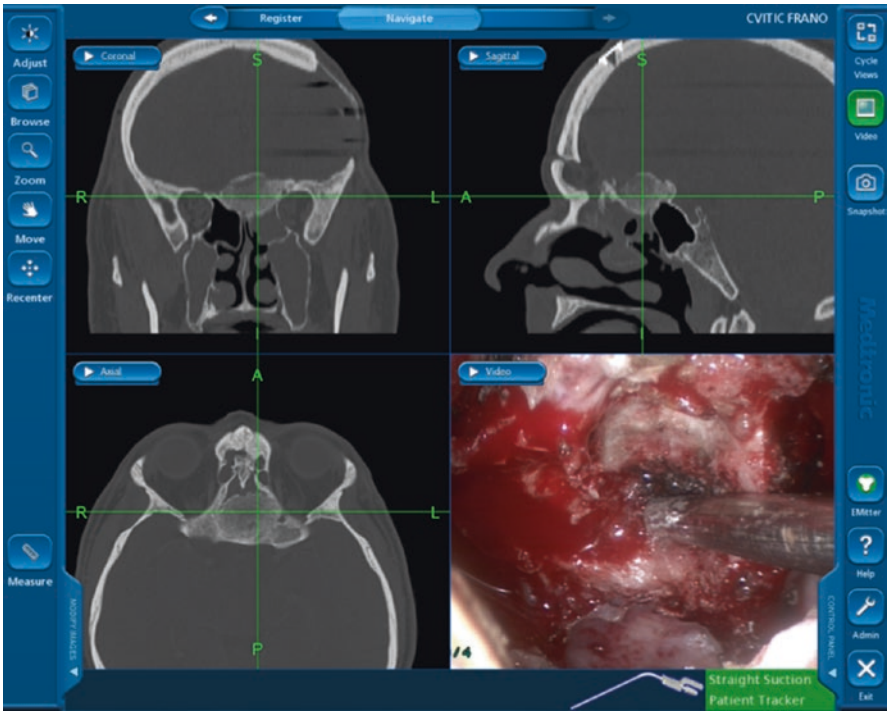

Fig. 17.3 The navigation system used during the endonasal endoscopic surgery of the anterior skull base. The point where the coordinates cross each other presents exactly where the top of the instrument is located

On the other hand, to use navigation system routinely, i.e., even in simple surgical cases, is unnecessary and leads directly to the development of less skilled endoscopic surgeons: without the navigation system, they could literally be lost in space. The surgeon must be able to understand at what exactly he or she is looking, what is the uncinate process, what is the ethmoidal bulla, how does the anterior wall of the sphenoid sinus look like, and how to approach to the bottom of the frontal sinus without help from navigation. Navigation should be used in particular clinical cases, mostly when it goes for transnasal endoscopic skull base surgery, optic nerve decompression, duraplasty endoscopic procedures, etc., i.e., for the surgical procedures which anyway require an experienced surgeon. Navigation system is not at all suitable for the beginners in FESS. There is no need to use navigation for the simple FESS; I would say routine surgical procedures.

17.4 Balloon Sinuplasty

Regarding balloon sinuplasty, I would say that it is just one more utensil within the armamentarium that an endoscopic sinus surgeon has on the table. In most of the cases, balloon sinuplasty is used as to "correct" the natural ostium of the maxillary

sinus. But, most of the articles obviously present the cases of Two Holes Syndrome, i.e., the defect of the fontanel, which otherwise can be easily endoscopically identified, and the balloon is inflated within the natural ostium (which in most of the cases is closed because of chronically swollen mucosa). What really happens is the same story as what some other endoscopic surgeon does using the backbiting forceps as to remove the tissue bridge that divides the defect of the fontanel and dysfunctional natural ostium of the maxillary sinus [6, 7]. In terms of that, balloon sinuplasty does not represent any advantage in the treatment of chronic maxillary sinusitis. The problem of improving the drainage of the frontal sinus is different in the sense that to do this properly and to have later on the permanent good result, the anterior at least partial endoscopic ethmoidectomy is required as to enable balloon catheter to be directed and placed to the ostium of the frontal sinus. In this very case, one should not forget that the lateral and particularly superior part of the infundibulum, like the lower section of the opening of the frontal sinus, could in some cases be in a close contact to the orbit; even more, it can be a part of the upper medial bony wall of the orbit when the frontal sinus is well or even very well pneumatized. So, to apply the pressure by inflaming the balloon blindly in these circumstances could be inappropriate.

In this moment, we have to ask ourselves: what exactly is the balloon doing to the surrounding tissues while inflamed? Just pushing them to make some more room for the sinus drainage and ventilation? If yes, how exactly does it happen? Are there any uncontrolled fractures of the surrounding bony elements? To my mind, the best option is to operate endoscopically, step by step, until the bottom of the frontal sinus becomes clearly visible. Balloon sinuplasty sounds great and, up to date, is an attractive utensil, but one should think twice before using this tool. To my mind, it goes for a step backward, not at all an advantage.

NHS UK states that:

> In a study of 115 patients, the balloon was successfully inserted in 347 out of 358 sinuses (97%). After 1 week, 232 out of 341 sinuses were clear (68%) and after 24 weeks, this had increased to 246 out of 304 sinuses being clear (81%). Two studies looked at symptom relief. A study of 1036 patients reported that 95% of patients had improved symptoms and 73% of patients were completely free of symptoms after an average of 40 weeks following the procedure. The study of 115 patients measured symptoms using a scale which ranged from 0 (least severe) to 5 (most severe). Before the procedure, the average score was 2.14. After the procedure, the average score had improved to 1.27. Another study of 70 patients, in which 35 patients had this procedure and 35 patients had a different procedure (called functional endoscopic sinus surgery), showed that the patients in the balloon group had greater improvements. Two studies looked at whether any further procedures were needed. Out of a total of 1145 patients, 28 needed a further procedure. [8]

17.5 Conclusion

There is no doubt that the invention of the CT scan and the Hopkins rod have increased our knowledge and understanding of sinus disease. Outcome measures in sinus surgery are complex [9] and have shifted in emphasis from those of the

operator such as endoscopic appearances, ostial patency, or CT scan changes to those of the patient. Eighty percent of respondents in a recent study of patients' and physicians' views on outcome measurement in CRS considered symptomatic improvement the most important [10].

Currently there is a randomized trial ongoing in the UK to evaluate the benefit of surgery over continued medical therapy in CRS patients who have failed an initial course of medical treatment.

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What Is the Significance of Rhinitis in Otitis Media with Effusion?

18

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18.1 Introduction

Otitis media with effusion (OME) is a condition in which the middle ear is chronically inflamed and retains fluid in the middle ear cavity. OME occurs in 15–20% of children [1] and is a key health problem in the paediatric population. It results in major financial costs, which are thought to run into billions of US dollars each year [2].

OME is also termed serous otitis media. It is a condition in which there is fluid (effusion) from the middle ear, but there are no features of acute infection [3]. Whilst OME is often referred to as "glue ear", this is only appropriate where the fluid has been occurring for a prolonged period and the middle ear contains viscous liquid with the consistency of glue. OME frequently follows an acute middle ear infection, but acute otitis media need not precede the condition, which can also arise if the eustachian tubes are not working [4].

The fluid in OME is non-suppurative and may be mucoid or serous. The sufferer from OME typically complains of auditory loss or aural fullness. Otalgia or pyrexia is not usually found. Hearing loss associated with OME in children is often so slight or insidious that it only becomes apparent on audiometry. In one particular type of OME, serous otitis media, a transudate forms when a pressure gradient abruptly forms, with lower pressure in the middle ear than outside. Serous fluid is watery and clear [5, 6].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_18

Being able to differentiate between OME and other infective conditions of the middle ear is vital [7]. The term "otitis media" encompasses any inflammatory pathology affecting the middle ear, without consideration of the origin or pathological features of the condition. Since the temporal bone contains pneumatised cavities which communicate freely with each other, when the middle ear becomes inflamed, it may spread into the open spaces represented by the mastoid, the perilabyrinthine air cells and the petrous apex. Several disorders, that have overlapping features, together make up otitis media: acute otitis media (AOM), recurrent acute otitis media (RAOM), OME and chronic otitis media with effusion (COME) [5].

18.2 Pathophysiology

The pathogenetic basis of OME remains only partly known. At present, it seems that numerous factors are involved. A number of triggers result in the same pathological process, in which inflammation, discharge and hyperplastic mucosa are the cardinal features. The persistent effusion comes about through a mechanism involving inflammation, innate immune defences, excessive production of mucus and epithelial hyperplasia. The traditional explanation for discharge in OME was that leftover fragments from lysed bacteria triggered persistent inflammation. It now seems this explanation is oversimplified [8]. Recent findings highlight the essential part played by biofilms in how the disorder develops [9–11]. Specimens obtained at operation are aseptic, but bacterial DNA has been shown by an immunofluorescent technique to be present. The DNA obtained mainly comes from non-typeable *Haemophilus influenzae* and was found on the middle ear epithelial surfaces. Impaired drainage of fluid in the middle ear [12, 13], inherited factors [14, 15], allergic reactions [16–22] and gastro-oesophageal reflux disease (GORD) [23] have also been considered to play a part.

For paediatric patients with OME who go on to have grommet insertion, around one in three cases has evidence of a specific pathogenic bacterium. This is especially so in patients under the age of 2 years [24–28]. Amongst the pathogens thus identified are three that usually produce acute otitis media: *Streptococcus pneumoniae*, non-typeable *H. influenzae* and *Moraxella catarrhalis*. Paediatric cases of chronic middle ear discharge may also be associated with infection by *Pseudomonas aeruginosa*, α-haemolytic streptococci and anaerobes [4].

Biofilms appear to be highly significant in the pathological mechanism leading to OME. Pathogenic organisms that can invade the ear produce biofilms, enabling them to remain and increase in numbers on the epithelial surface of the middle ear. In such situations, bacteriological culture may be negative. The evidence for biofilms in OME comes from various sources: observational research with an animal model, in which viable bacterial microorganisms were demonstrated within the biofilm [9]; isolation of DNA, mRNA and freshly synthesised proteins of bacterial origin in liquid extracted from the ear in OME [11]; biofilm appearances seen on biopsies taken from the middle ear in cases of grommet insertion for OME +/− recurrent otitis media; and no biofilms being seen in control biopsies obtained from paediatric cochlear implantation cases [4, 10].

GORD has been implicated in the pathogenesis of OME, according to one theory, but a definite causal link has yet to be demonstrated empirically. A systematic review that examined 15 studies concerning gastro-oesophageal or laryngopharyngeal reflux and middle ear infections noted that the frequency of GORD was seemingly higher in paediatric cases of OME than in the general paediatric population [4, 23].

OME may supervene in cases of AOM following resolution of the initial acute inflammatory response. In paediatric cases of AOM, up to 45% suffer from effusion or discharge 1 month after the episode resolves. However, only 10% still have fluid at the 3-month mark [5].

18.2.1 Classical Theory

There are two principal hypotheses as to why AOM occurs. The classical explanation posits an abnormally functioning eustachian tube as a condition sine qua non of AOM. It has usually been considered that the eustachian tubes fulfil three principal roles: they balance the pressure between the middle and external ear, they allow drainage of secreted material, and they defend the middle ear. A variety of factors may lead to a non-functioning eustachian tube, including anatomical anomaly, allergic-type inflammatory responses, upper respiratory tract infections (URTI) and physical injury [5].

When the eustachian tubes cease to function adequately, a lower pressure may occur within the middle ear as both nitrogen and oxygen in the middle ear diffuse away across the middle ear epithelium, lowering the gas pressure. Should this situation persist for a prolonged period, this pressure gradient causes transudation from the mucous membrane. The transudate will build up over time and will consist of a serous exudate without infection. However, the non-functioning eustachian tubes mean a lake of serous fluid develops, highly suited to culture any pathogenic bacteria present. In this way, AOM will result. One drawback with this explanation is that numerous researchers have proven experimentally that the same bacterial pathogens are responsible for both OME and AOM [5].

18.2.2 More Recent Hypotheses

More recently, it has been hypothesised that inflammation occurs in response to bacterial microorganisms that are present in the middle ear from the start of the process. Bluestone and other researchers have demonstrated, using imaging techniques, that paediatric cases of otitis media are associated with reflux upwards along the eustachian tube [29]. Beyond this, Crapko et al. [30] were able to show that pepsin had entered the middle ear cavity in 60% of paediatric OME cases. It is noteworthy, however, that refluxed pepsin is not unique to OME cases, as it can also be found in some healthy children [5].

O'Reilly et al. [31] discovered further evidence suggestive of a link between reflux and middle ear disease. A study with a prospective methodology examined

129 children suffering from otitis media, who had myringotomy and grommet insertion. Sixty-four of these cases had evidence of pepsin A in the ear cavity, showing that stomach contents had refluxed into the nasopharynx. The researchers explained this as evidence that reflux either provoked an inflammatory response or worsened already established inflammation.

18.3 OME and Allergy

The role of allergy in the pathogenetic mechanism producing OME is the subject of debate amongst researchers. Observational-type research has established that allergic rhinitis (AR) and OME are associated [16–21]. Furthermore, it has been shown that markers of allergy (IgE, mast cell activation, tryptase and myeloperoxidase) are present in the middle ear space in cases of OME [17, 22]. Despite this finding, when an animal model of OME was used, introducing allergens into the ear alone did not result in the formation of an effusion [32]. Topical nasal corticosteroids, whilst beneficial in AR, produced no benefit in cases of OME in some trials [4, 33] but did reduce the need for grommet insertion in another well-conducted double-blind study over 2 years [34]..

Allergic disorders (AR, atopic dermatitis and asthma) are more common in individuals with OME [35–40]. The pathogenesis of OME in atopic individuals has been proposed by some investigators to depend on a Th2 cell-mediated response. Sobol et al. compared the composition of effusions between cases of OME with and without allergy [41]. They found that the effusions in the allergy sufferers had more abundant eosinophils and T cells and the levels of cells producing mRNA transcripts for interleukins 4 and 5 were also elevated. The components that constitute the inflammatory response seen in allergic otitis media therefore resemble those found in late-stage allergic disease elsewhere in the respiratory system, e.g. in chronic sinusitis, AR or asthma [42, 43].

Nguyen et al. [44] have been able to demonstrate that the allergy-associated inflammatory response in paediatric cases of OME with known atopy is not just in the ear cavity itself but is instead spread evenly at each pole of the eustachian tube, i.e. middle ear plus nasopharynx. The cellular composition and pattern of cytokine response observed were similar to those seen elsewhere in the respiratory tract and corresponding to the late-stage inflammatory response seen in asthma, AR and chronic sinusitis when associated with atopy [41–43].

18.4 OME and Allergic Rhinitis

Given the high prevalence of both OME and AR in young children, the two conditions may sometimes co-exist in the same child. Studies performed clinically and experimentally have frequently concluded that allergy alone cannot lead to middle ear effusions. The reasoning is that, whilst allergic inflammation of type 1 can result in abnormally functioning eustachian tubes, this effect is usually short-lived, except

in perennial rhinitis. However, where the eustachian tube function is affected by allergy, effusions are not effectively drained [45].

Kreiner-Møller et al. [46] investigated 291 children aged 5 years who were part of the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) 2000 birth cohort. Thirty-nine per cent of the group suffered from OME, and there was an association with AR (adjusted odds ratio = 3.36, CI = 1.26–8.96, p = 0.02). This association, however, did not hold for nasal mucosal oedema, eosinophilia within the nose, non-allergic rhinitis, asthma or atopic dermatitis. The association between OME and AR reached a high level of statistical significance. Having AR meant a far higher risk of concomitant OME (OR > 3). The investigators reached the conclusion that OME has a close association with AR, probably due to a shared pattern of allergic-type inflammation, but there was no association with oedema occurring in the nose per se.

To explain the link between OME and AR, we can posit either a mechanism of local allergy in the respiratory-type epithelium within the middle ear space or an inflammatory response induced by malfunctioning eustachian tubes or conclude that the pathogenesis is currently unknown. One probable pathogenetic mechanism is for the initial event to be the eustachian tube ceasing to function on account of oedema associated with allergic-type inflammation in the respiratory epithelium, followed by secondary inflammation in the ear itself [47].

It was first noted that chronic OME (COME) and AR were related when a subgroup of individuals with OME that was refractory to the usual pharmacological treatments was examined more closely. AR was common in this subgroup. There have been multiple studies that noted the high prevalence of AR in OME patients and thus found an epidemiological link between COME and allergy. An example is the study by Alles et al., where 89% of COME cases were found to have concomitant AR [16]. Notably, this prevalence greatly exceeds that found in the general population, i.e. between 10 and 30% of adults and between 20 and 40% of children [48, 49]. Alles et al. examined children aged between 3 and 8 years attending a "glue ear" clinic for symptoms related to the nose. The definition of AR they employed called for two symptoms involving the nose (e.g. sternutation, nasal pruritus or an allergic crease) or one nasal symptom plus other evidence of AR (i.e. positive skin prick testing or nasal eosinophilia) [50].

When they enquired about symptoms related to AR, the researchers discovered that 5.1% of the group had a history highly likely to represent AR and a further 31.5% had one symptom or more from a list of those expected to occur in AR. These results are in line with expectations, given the previously reported prevalence of AR [51]. 32.8% of the sample had symptoms related to the ear. Symptoms related to the ear and those related to the nose were cross-tabulated, which identified the fact that AR and otitis media were associated at the level of statistical significance ($p = 0.000$) [51]. The prevalence of AR in patients with COME has alternatively been reported to be somewhat less than the 89% reported by Alles et al. A Brazilian study examined a group of 51 individuals suffering from COME aged between 3 and 55 years, all of whom underwent ear surgery. The researchers looked for evidence of AR or NARES (non-allergic rhinitis with eosinophilia) in the patients, finding 33.3% to

have AR and 15.7% to have NARES. Their conclusion was that nasal allergic conditions and COME were related [50, 52].

According to Caffarelli et al. [53], the prevalence of AR in paediatric COME was a mere 16.3%, when symptoms involving the nose but not related to an infection were the criteria for diagnosing AR. The prevalence of AR in cases of COME (16.3%) was, however, significantly different from that of geographically matched healthy controls (5.5%) [53].

Hurst and Venge [54] demonstrated a raised level of eosinophil cationic protein (ECP) (indicating eosinophilic activation) in children with allergic disorders who had COME, compared to the ECP level in COME children without allergy. ECP was more elevated in effusion fluid than in the patient's serum. The level of myeloperoxidase (extracted from mast cells) was also elevated in effusion fluid from paediatric cases with objective documentation of allergy than in those with no allergy. The difference was statistically significant. Wright et al. [55] showed that mRNA transcripts for interleukin 5 were greater in paediatric cases of COME with allergy than in controls. Notably, there was no difference in serological titres of IgE between cases and controls in this group. Hurst [50, 54–61] deduced, on the basis of such research reports concerning the level of Th2-associated cytokines in children with COME who were also atopic, that COME differed greatly between children with allergy and those without.

18.4.1 The Unified Airway Model

The histological features of the epithelium of the upper and lower airway are identical to that of the middle ear, i.e. pseudostratified ciliated columnar epithelium. The histological appearances in inflammation affecting the bronchi in an asthma attack and those affecting the middle ear are similar. In both cases, the mucosal epithelium deepens, the numbers of goblet and columnar cells increase, and mucus production is stepped up [62]. There is an eosinophilic infiltrate containing T helper cells. This infiltrate concentrates around follicles, with a similar appearance to the MALT (mucosa-associated lymphoid tissue) found nasopharyngeally and in the bronchi [63]. In addition, the middle ear can mount an allergic reaction, similar to the airways, as shown by Hurst et al. These researchers found that mast cells in the middle ear degranulated actively and tryptase (a marker of mast cell activity) was raised in effusion fluid collected from the middle ear [60, 64]. In patients with allergic disorders who experience COME, the Th2-associated cytokines (interleukins 5, 10 and 13) are raised, just as they are in asthma or AR [50].

18.5 Conclusion

The precise aetiology of otitis media with effusion remains unclear, and the pathogenesis is no doubt multifactorial. Recent research demonstrates that gastro-oesophageal reflux and biofilms may possibly play important roles. Nonetheless,

allergic rhinitis and the allergic reaction remain strongly associated with OME in paediatric patients, and the unified airway model lends credence to a potentially causative association.

This chapter has focused on children, in whom OME is common. In adults, OME is rare but may be associated with significant and severe rhinosinusitis, such as NSAID-exacerbated respiratory disease (N-ERD) or eosinophilic pauci-granulomatous arteritis [65].

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19 Is There Any Analogy Between the Defect of the Eardrum in Chronic Otitis Media and Defect of the Fontanel (Two Holes Syndrome) in Chronic Maxillary Sinusitis?

Ranko Mladina

19.1 Introduction

Yes, there is a great analogy between the defect of the eardrum in chronic otitis media and defect of the fontanel, the so-called Two Holes Syndrome (THS), which is just one of the forms of the chronic maxillary sinusitis! One should know that when speaking of maxillary sinus and the middle ear as cavities inside human organism, it goes for the same specific "volcanoes," constantly threatening with their possible eruption. The dimensions of these two volcanoes are very different, i.e., while the middle ear consumes about 1 cm^3, the volume of the maxillary sinus varies from 3 up to 7 cm^3. But regardless of the difference in dimensions, both spaces are supposed to be hidden from outside world. First of all, they naturally intend to have their own, undisturbed ventilation which enables the constant equation of the air pressure between the particular pent space and the outside. In case the ventilation does not function properly, the physiology of the respiratory epithelium, which covers both sinuses and middle ear chamber, will be significantly disturbed in the sense of slowing down or even stopping mucociliary clearance. This is the first analogy. In addition, this means that the cleaning and discharging of the physiologic contents that both maxillary sinus and middle ear produce constantly simply become irregular. It happens owing to the active life of the seromucinous glands located within the stroma of the epithelium within both the middle ear and maxillary sinuses. This is the second analogy. The mucosal secretion is essential for the function of the mucociliary system in every respiratory epithelium in general, as to produce the obligatory mucosal blanket, always placed on the top of the cilia. In other words, disturbed ventilation leads directly to disturbed drainage. The maxillary sinus ventilates itself through the natural ostium in all cases when it is healthy and undisturbed in any sense. The drainage happens through the natural ostium as well and slowly travels to the nasal cavity, comes out, and proceeds toward the pharynx.

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_19

The middle ear is supposed to ventilate through the Eustachian tube which, in fact, is not a constantly open pipe, but an elastic virtual tube that opens owing to deglutition or jaw movement. Two muscles are responsible for the quality of opening up of the orifice of the Eustachian tube: *tensor veli palatini* muscle and *levator veli palatini* muscle. There is also a *salpingopharyngeus* muscle, but it seems its function is just accessory, not crucial in the process of opening up of the tube orifice. So, regarding the openings, maxillary sinus has more or less static natural opening which does not depend on the function of any muscles, while the middle ear has a more complicated opening, i.e., Eustachian tube, a virtual pipe, which opens from time to time according to the action of the abovementioned muscles. Therefore, there is no analogy between the middle ear and maxillary sinus in regard to ventilation and drainage.

19.2 What Happens in Case Some of the Ventilation-Drainage Systems of These two Anatomical Entities, Maxillary Sinus and Middle Ear Cavity, Fails?

19.2.1 Maxillary Sinus

If there is no any ventilation of the maxillary sinus, the mucociliary system slows down or stops by time, and mucus is accumulating inside the sinus space with no prospect of being drained from the sinus. Once the quantity of the accumulated mucus is enough to make a constant pressure over the maxillary sinus walls, there are two options to let this mass get out: (a) natural ostium (only in theory since all this happened because the ostium already has been blocked, so it can't allow any discharge) and (b) the fontanels. Fontanels resemble very much the eardrum: they are elastic, and their structure is similar to the eardrum, since the eardrum has two layers (one is middle ear mucosa, and the other is epidermis of the meatus, whereas the fontanels are built by the mucosa of the nasal cavity and the mucosa of the maxillary sinus). This means the fontanels don't have any bone between two mucosal layers and thus they represent a specific *"locus minoris resistentiae"* (from Latin: the place of minimal resistance or weak place). In case of emphasized accumulation of the contents within the space of the maxillary sinus, and the contents are there because the natural ostium has been blocked and firmly closed, the only chance to deliberate poor sinus is the "eruption" of the "volcano," which in this very case is the fontanel of the related maxillary sinus. The fontanels of the maxillary sinus may have been created during evolution by saving certain prehistoric people from empyema of the maxillary sinus. This disease if untreated can directly lead to death. In prehistoric times, the rupture of the fontanel most probably has saved a lot of lives. But, there is a problem with the fontanels: they do not spontaneously close—there is no cicatrizing in case of ruptured fontanel. The result is the permanent defect of the fontanel which, unfortunately, has been widely but, at the same time, completely wrongly called "accessory ostium."

Well, once we have the defect of the fontanel, the contents finally get out of the maxillary sinus, a kind of ventilation (through the opening of the fontanel) starts again, and the circumstances for the healing of the natural ostium are real and can be employed in terms of that. But, if so, what the rhinologist can see during the endoscopy of the nose is the defect of the fontanel (Fig. 19.1)! CT scanning of the paranasal sinuses might also clearly show the defect of the fontanel (Fig. 19.2).

The natural ostium of the maxillary sinus cannot be seen during nasendoscopy in the unoperated patient since the uncinate process hides it, but still, the existence of two "holes" on the medial wall of the maxillary sinus can be relatively easily identified on both axial and coronal CT scans of the paranasal sinuses (Fig. 19.2). The main prerequisite to identify the defect of the fontanel on CT scans is to know what the defect looks like radiologically and check for it. If the CT scan is observed by someone unaware of defects of the fontanel nor where the natural ostium of the maxillary sinus is found, then the chances to identify anything "unusual" are minimal.

Just a few words regarding the term "accessory ostium": the adjective "accessory" implies something that stays nearby, for any case, to be of a help if needed, something that could be considered as "additional," almost being physiological. But, the "accessory ostium" we are talking about in cases with obvious defect of the fontanel should not be considered as an additional ostium simply because it is not the ostium. It is a defect of the fontanel, i.e., the same story as the defect of the eardrum in cases of chronic otitis media. It does not help the maxillary sinus in any way, so there is no reason to name this anatomical entity as "accessory ostium."

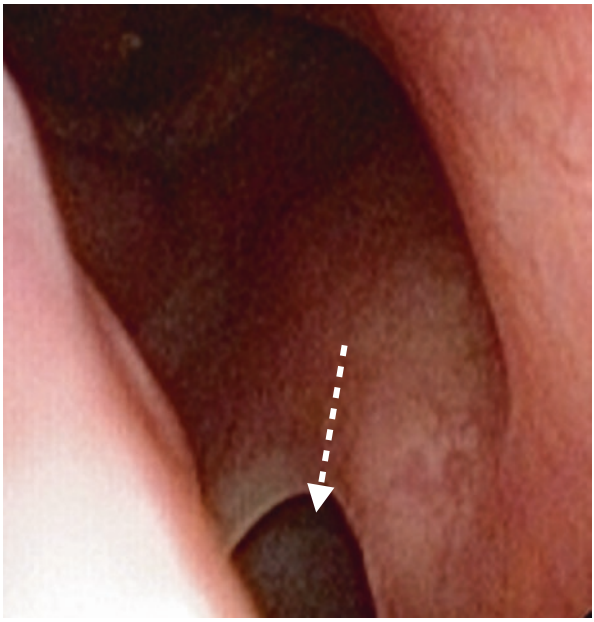

Fig. 19.1 Left nasal cavity. The defect of the posterior fontanel is clearly seen (white dotted arrow)

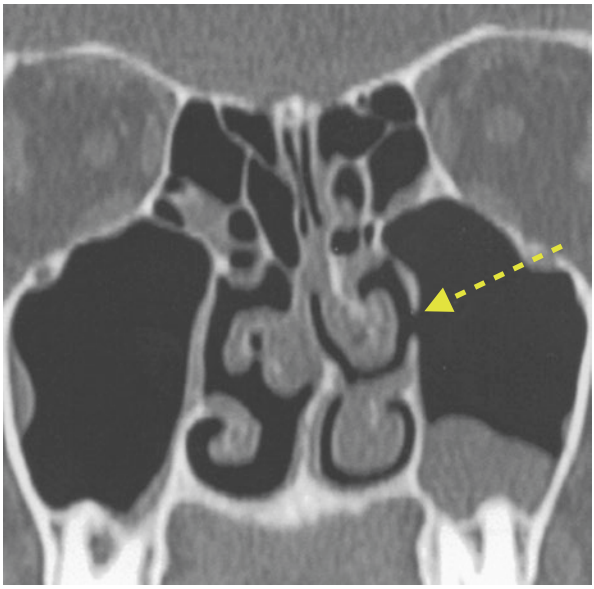

Fig. 19.2 Coronal CT scan of the paranasal sinuses. The dotted yellow arrow indicates the defect of the fontanel

So, what are the consequences of having two openings on the lateral nasal wall instead of one natural maxillary sinus ostium? The consequence is so-called Two Holes Syndrome (THS) [1, 2]. For illustration, Mladina found that in the cohort of even 8879 patients suffering from chronic rhinosinusitis (CRS), the THS has been found in even 1713 (19.3%). In addition, in 1442 healthy volunteers, THS was found in only 7 of them, i.e., 0.48%! More than 71,2% of the people suffering from the postnasal drip in fact suffer from the recirculating mucus, i.e., of the Two Holes Syndrome (THS). What really happens is the recirculation of the mucus: the sinus mucociliary clearance system recuperates from the inflammation and works well, pushing slowly the mucus toward the natural ostium. The mucus comes out from the sinus and starts the usual way toward the nasopharynx. In some certain moment, it simply starts to disappear, to "fall down." Where? In the trap! And the trap is the hole in the fontanel! In this very moment, mucus finds itself again in the maxillary sinus. What the maxillary sinus does is pushing this "new" amount of the mucus through the natural ostium again. It works well! But, the problem is that the mucus returns time and again, and the final result is the real mucous hank which slowly rotates around the tissue bridge that divides the natural ostium of the maxillary sinus and the defect of the fontanel. In a certain moment, the mass of this specific mucous hank reaches the ultimate dimensions and weight which enable a part of it to be rejected. Owing to the gravitation, the rejected mucus is always directed toward the nasopharynx. The first swallowing of the just arriving part of the mucus, detached from the hank up there in the ostiomeatal complex, is the beginning of the postnasal discharge. Vast majority of the patients suffering from THS have the leading symptom of the postnasal drip and vice versa.

The treatment of chronic maxillary sinusitis presented as THS is quite simple: endoscopic intervention in the region of the tissue bridge that divides natural ostium of the maxillary sinus and the defect of the nearby fontanel. The backbiting forceps

perfectly serves to remove the "tissue bridge" and thus to form the unique maxillary sinus opening, i.e., the so-called middle antrostomy. Once there is no more tissue bridge, there are no chances for the recirculating of mucus, coming from the maxillary sinus, returning into the sinus owing to falling inside it through the "trap" (defect of the fontanel), coming out again owing to the forces of the still active mucociliary clearance system, and so on, until the mass of the specific mucous hank reaches the ultimate dimensions and the weight which enable a part of it to be rejected, owing to the gravitation directed toward the nasopharynx. The first swallowing of the just arriving part of the mucus, detached from the hank up there in the ostiomeatal complex, is the beginning of the postnasal discharge. The disease of the related maxillary sinus immediately stops. In cases of THS, one should be cautious when studying the CT scans, not only because of the attempts to identify the defects of the fontanels but also because, in vast majority of THS patients, the changes of the bony walls of the maxillary sinus can be observed in the sense of being more thick. The thickness of the bone in this very case comes because of chronic irritation that comes from the closest neighborhood, and it is periosteum. The mucosa of the maxillary sinus can be healed properly owing to antibiotics, but sometimes the traces of the inflammation drop behind within the tissue of the periosteum. It has its name: chronic maxillary periostitis. Nobody speaks about this clinical entity; it is almost unknown or intentionally forgotten. And, the direct consequence of the long-lasting chronic periostitis of the maxillary sinus is the thickening of its bony walls. Once we can see something like this on the CT scans, we can be sure we are dealing with chronic maxillary sinusitis (chronic osteitis). It seems to be a smoldering chronic infection and should not be neglected. It could be a hidden and in very many cases undiscovered origin of so-called focalosis! For those who don't know this fact, to see "black spaces" in the region of the maxillary sinuses on the CT scans will be a "normal radiological finding." And this is simply wrong! Figure 19.3

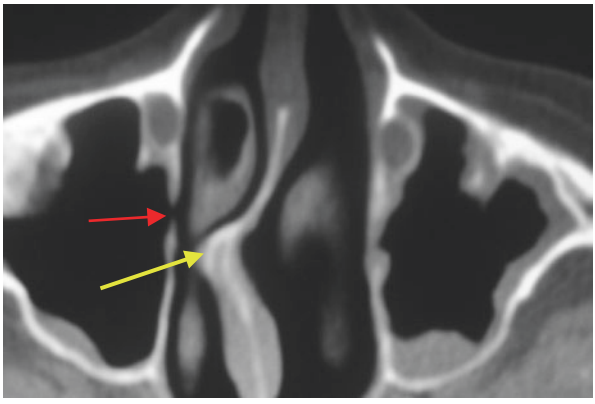

Fig. 19.3 An axial CT scan of the maxillary sinuses showing several abnormalities: the defect of the fontanel of the left maxillary sinus (red arrow); severe septal deformity combined of type 5 and type 3, both to the left side (yellow arrow); and thickened maxillary sinus bone (no needed arrows) indicating an underlying osteitis beneath the sporadically edematous mucosal areas

presents an example of the chronic osteitis of the maxillary sinus which could be classified as grade A according to Cierny classification [3].

In most of such cases, endoscopic sinus surgery techniques cannot help entirely since drilling out of the superficial layer of the diseased bone is required as to eliminate the disease entirely. The osteoplastic approach to the maxillary sinus is absolutely indicated in such clinically difficult cases.

The question of antibiotics remains relatively unsolved. It seems that currently only clindamycin can penetrate infected bone. This is not an official statement, but merely a result of clinical experience.

But, what about Eustachian tube dysfunction? How can we diagnose this problem? Is the tympanogram finding relevant to judge about that? Or, maybe a kind of tubo-fiber endoscopy will be better and more informational? What about saccharine test of the Eustachian tube?

Well, from the diagnostic point of view, to perform the tympanogram seems to be very useful in the sense of obtaining reliable information of the eardrum status, i.e., how elastic it is. In cases of hypotensive aerodynamic circumstances within the middle ear, the eardrum will be uptight and more concave looking from outside. The hypotensive aerodynamic circumstances are the result of the dysfunction of the Eustachian tube.

19.2.2 Chronic Otitis Media

As stated before, the middle ear, however, has a Eustachian tube, both for ventilation and equalizing of the air pressure and for drainage. Unfortunately, there are no recent scientific data on the histological appearance of the mucosal lining of the Eustachian tube. The last relatively reliable data related to the morphology of the Eustachian tube belong to the last century [4–6]. For instance, the photographs of the epithelium of the Eustachian tube are in general not available in the literature. Furthermore, saccharine test belongs to the routine methods in rhinology [7, 8]. This test also has been used in the last 40 years to test the mucociliary clearance function of the Eustachian tube many times but (there is always some "but"), exceptionally, in patients suffering from chronic otitis media with perforation, which means in patients that already haven't had normal function of the Eustachian tube. Otherwise, the chronic otitis media would not have appeared [9, 10]. Here we have again the analogy between the chronic maxillary sinusitis and chronic otitis media with perforation: perforation of the eardrum is the sign of eruption of the "volcano." The purulent or pathologic discharge found a way out, a kind of "emergency exit," by rupturing the tympanic membrane, but, as in the case of the fontanel at the lateral nasal wall, which does not have any mechanism to close spontaneously, or the eardrum also does not have any natural mechanism to close spontaneously—almost the same story as in the case of chronic maxillary sinusitis, particularly THS.

To perform the saccharin test in subjects that are not otologic patients, but healthy volunteers, hypothetically by means of otomicroscopic microinjecting of "one

drop" of the saccharine solution through the intact eardrum (local, superficial anesthesia is required, of course) within the middle ear, and then to wait for the appearance of the sweet taste in the throat of the examined person, this perhaps would be a proper and objective measurement, but only somewhere in the future. An experienced, brave, and enthusiastic ear surgeon will be the one to try this: to make a step forward and elucidate this area for all others, who are just seating quietly in their chairs and waiting.

Khamapirad couple [11] many years ago were brave enough and tried with so-called cine eustachiography, but it was obviously just a nice try to present cinematographically the internal life of the Eustachian tube epithelium. Poe et al. (2000) tried with the video-endoscopy, but it seems the endoscopy was not related to the inland of the tube itself, particularly not to the opening of the tube in the middle ear cavity, but mostly to the orifice of the tube in the nasopharynx [12]. Finally, there was a nice try by Klug et al. [13] of the endoscopy of both Eustachian tube and middle ear (for the first time from inside view) but again in cadavers. Therefore, there are no further reports on this technique, particularly not in living persons. Most recently there are reports, not published yet, about the high-tech fiber endoscopes of 1 mm in diameter with the laser microcamera inserted just behind the objective. Such a product maybe will be convenient to perform the first tuboscopy in a live subject, most probably coming from the opposite nasal cavity as to have more space for the maneuvers of the fiber endoscope and to be as precise as possible. Most probably it will be performed in a "four-hand" technique, i.e., another doctor will be waiting at the level of the choana of one nasal cavity to see the thin endoscope approaching "his" area from the other nasal cavity. Maybe some instrumental help will be required also while inserting the thin fiber endoscope in the tube orifice and further within the tube itself. Time and again, some similarities with the colonoscopy and insufflations of the air to dilate the colon and other parts of the bowels perhaps will be applied also here since Eustachian tube seems to be just a virtual tube that in healthy people opens very shortly, just for a second, i.e., just during the deglutition or jawing. There are not reliable data on this matter in the literature so far. Neither, as previously stated, there are reliable data on the histology of the epithelium that lines the Eustachian tube in live person. These are the facts that we are terribly missing.

In case the tuboscopy will be finally realized and become the routine method of examination, the placing of some kind of stent will become a reality in all those who suffer from inactive or inadequately functioning Eustachian tube. However in post-polio subjects, a chronically patent (patulous) Eustachian tube is problematical, giving annoying symptoms of echoing of one's own voice (autophony), so a stent is probably not a good idea. The function of this tube is essential. All cases of chronic otitis media, be it with effusion (OME) or with perforation of the eardrum (COM), are essentially based on the dysfunction of the Eustachian tube. The grommets, the fantastically performed tympanoplasties, etc. are just solving the consequences, without even touching the essential cause of the disease.

19.3 Conclusion

So, at the end, there is no analogy regarding the treatment of the chronic maxillary sinusitis, i.e., THS, and chronic otitis media with the perforated eardrum. The first entity could be healed by the previously mentioned endoscopically performed middle antrostomy, sometimes with a little help of specific antibiotics which penetrate the bone (in cases with chronic periostitis or even chronic otitis), but the second one, the middle ear, should have to wait for some essential changes in solving the essential problem, i.e., the site where the disease starts: Eustachian tube. Only after that we will be able to say that the battle has been won. And perhaps there will be on the horizon a kind of an additional, new analogy between the chronic maxillary sinusitis, particularly THS, and chronic otitis media with the eardrum defect.

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Approaches to Repairing Skull Base Defects for the Prevention of Cerebrospinal Fluid (CSF) Leakage

20

Faruk Altınel, Ali Arslantaş, and Jeffrey Janus

20.1 Introduction

Cerebrospinal fluid (CSF) rhinorrhoea refers to any situation wherein CSF leaks nasally. This occurs when the subarachnoid space is in continuity with the nose as a result of a gap in the arachnoid and dura mater and some discontinuity of the bony structures of the skull. It is frequently a complex matter to assess and treat CSF rhinorrhoea. Laboratory assessment of nasal discharge to show whether CSF is present is not invariably accurate, whilst imaging may fail to demonstrate leakage that comes from a small hole or may not reveal several simultaneous sites whereby CSF leakage is occurring. Due to these limitations, unwarranted surgery and insufficient interventions have both occurred [1].

It appears that Willis was the first to note CSF rhinorrhoea, which he did in 1676 [2, 3]. In 1826, Miller noted a fistulous connection between the nose and the subarachnoid cavity in a child with hydrocephaly. The patient had complained of watery rhinorrhoea from time to time, and the fistula was noted at autopsy. Miller is considered the first to provide a full characterisation of CSF leakage. St. Clair Thompson extended Miller's work in 1899 by noting that CSF leakage could occur through both trauma and spontaneously [3, 4]. Ommaya and colleagues (1968) then offered a tripartite division, with one traumatic and

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_20

two non-traumatic types. The non-traumatic types were subdivided on the basis of normal or elevated CSF pressure [5].

Although it rarely occurs, CSF rhinorrhoea can have grave complications, resulting in both morbidity and mortality. CSF leakage happens when there is a breach in the structures that normally separate the anterior and middle cranial fossae from the nose and sinuses. Since there then exists a portal of entry for pathogens into the central nervous system (CNS), a wide range of serious complications may occur, including the possibility of long-term disability and, indeed, death.

CSF contains water, electrolytes (Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^-, and HCO_3^-), glucose (at a level 60–80% that of the serum), amino acids, and a number of proteins (22–38 mg/dL). CSF is clear and without colour. There is usually no cellular component, i.e. there are less than five polymorphonucleocytes or mononucleocytes in each microlitre.

The bulk of CSF production (i.e. 50–80%) occurs in the choroid plexus. The outer ependymal layer can produce approaching 30%, with capillary ultrafiltration accounting for a maximum of 20% of daily requirements. CSF is manufactured as an ultrafiltrate of blood produced by the choroid plexus epithelium found surrounding the ventricles of the CNS. Sodium is actively transported by Na^+/K^+ ATPase across the basal layer of the epithelium, which sets up an osmotic gradient favouring water movement into the epithelium. Within the epithelium, HCO_3^- ions are generated by the action of carbonic anhydrase. An apically located Na^+/K^+ ATPase then pumps sodium into the ventricular lumen, the gradient again favouring movement of water in the same direction. This process results in CSF being formed within the ventricles.

The total volume of new CSF in a day is around 500 mL, at an hourly rate of 20 mL. On average, the CNS contains between 90 and 150 mL of CSF. CSF circulation begins at the choroid plexus, within the lateral ventricles. The fluid passes through the aqueduct of Sylvius to enter the third ventricle. The foramen of Luschka and the foramen of Magendie allow CSF to circulate through the fourth ventricle and emerge in the subarachnoid cavity, whence the arachnoid villi are responsible for its removal from the CNS.

There is a pressure gradient between the site of production and the site of reabsorption of the CSF, which accounts for the circulation of CSF. The range of normal CSF intracranial pressure (ICP) is between 10 and 15 mmHg, with a pressure above 20 mmHg indicative of abnormality [6].

20.2 Anatomy

The anatomical location of the majority of spontaneous CSF leaks depends on where the anterior cranial fossa is naturally weakest or where a surgical operation contributes to weakening of the skull. Around 40% of CSF leakage occurs via the lateral lamella of the cribriform plate. Weakness around the frontal sinus accounts for 15% of cases. Fifteen per cent of leaks occur near the sella turcica or the sphenoid sinus.

Iatrogenic trauma during endoscopic sinus surgery frequently affects the lateral lamella of the cribriform plate or the roof of the ethmoid posteriorly in the vicinity of the anterior and medial sphenoid wall. An infrequent presentation is where the middle or posterior fossa has been breached and CSF enters the nose after passing through the middle ear compartment and dripping down the eustachian tubes. In such cases, the patient usually complains of fullness in the ear, resulting from a middle ear effusion containing serous liquid [6].

20.3 Aetiology

CSF leaks fall into the following categories: trauma-related, iatrogenic, and spontaneous (in other words, idiopathic). Trauma to the face (which can be blunt or penetrating in character) may lead to CSF leakage. Surgical oncological operations (either ENT or neurosurgery) may result in iatrogenic leaks, as may functional endoscopic sinus surgery (FESS). The majority of cases which would previously have been classed as essential are currently considered likely to be due to raised ICP, as occurs in idiopathic intracranial hypertension (IIH). Anomalous congenital skull malformations and particular neoplasms may also result in CSF discharge through the nose [7].

Lobo et al. reviewed the published research to identify factors increasing the risk of spontaneous CSF leakage. They confirmed that, as well as raised ICP, being obese, being female, and suffering from obstructive sleep apnoea (OSA) all put up the risk of CSF rhinorrhoea. Some 72% of cases of spontaneous CSF leakage were in women, and 45% were in OSA sufferers [8].

20.3.1 Traumatic CSF Rhinorrhoea

Ninety per cent of the overall time, CSF leakage is due to closed or penetrating traumatic injuries to the skull. If the nasal discharge occurs within 48 hours of injury, it is termed “immediate”, after which cases are “delayed”. The bulk of those who have CSF leaks following an accident (such as a road traffic accident) fall in the immediate category. On the other hand, delayed presentations mostly (95%) occur less than 3 months after the trauma was incurred [6].

20.3.2 Iatrogenic CSF Rhinorrhoea

Unlike the situation in traumatic CSF leakage, iatrogenic CSF leakage only becomes apparent after less than a week in 50% of individuals. Thus, the majority of these patients will have already left the hospital by the time the leak is noticed, and it is therefore vital that patients are aware of what to look out for in a CSF leak, i.e. a salty or metallic taste in the mouth.

Surgery of any kind in the vicinity of the base of the skull may inadvertently lead to CSF leakage. The range of trauma which is implicated covers everything from

straightforward crack formation in the bony plates to major (>1 cm) gaps in the bone, leading to damage to the dura mater and potentially the brain itself.

The anterior base of the skull is most vulnerable to iatrogenic trauma during FESS at the thin lateral lamella of the cribriform plate. The highest portion of the ethmoid roof posteriorly and the posterior aspect of the frontal recess are likewise frequent sites for iatrogenic injury to occur.

20.3.3 CSF Rhinorrhoea Related to Neoplasia

Expanding benign tumours are rarely a cause of CSF discharge through the nose. Malignant tumours and tumours that exhibit an aggressive growth pattern locally (such as inverted papilloma) are a different matter, as they can cause osseous destruction in the anterior cranial fossa. Enzymes are released which result in loss of the bone structure and an inflammatory response. The dura mater may become involved. Resecting such a lesion may well lead to an immediate-type CSF leak, even if the lesion itself has not already produced one. Thus, surgeons should take precautions to enable them to effect an immediate repair of the leak, which may be done by a transcranial approach or by means of the endoscope.

20.3.4 Congenital CSF Rhinorrhoea

A rare cause of CSF leakage is where the anterior neuropore fails to close completely, leading to a situation where nervous system cells herniate through the anterior cranial fossa. The usual problem is that the fonticulus frontalis or foramen caecum has failed to close. A meningoencephalocele may become apparent in a child when there is a mass present, either within or outside the nose, and the mass both transilluminates and gets larger when the child begins to cry, known as the Furstenberg sign. Clinicians need to be alert to the possibility of a meningoencephalocele in cases where a mass is present within the nose, especially if found in the midline. No attempt to biopsy the mass should be made until a full radiological evaluation has occurred.

20.3.5 Spontaneous CSF Rhinorrhoea

Spontaneous CSF leakage from the nose refers to a situation where no apparent triggering cause has been identified. Whilst this definition tends to imply the occurrence is essential in nature, recently it has been shown that there is in fact a latent cause: raised intracranial pressure (ICP). ICP may result from a number of different processes; however, CSF rhinorrhoea is mainly linked to idiopathic intracranial hypertension (IIH). A further possibility is ICP secondary to obstructive sleep apnoea [9].

20.4 Pathophysiology

Immediate traumatic CSF leakage occurs when there is both a flaw within a bone and the dura matter has been torn. One way in which traumatic CSF leakage might be delayed is where undamaged dura mater has gradually emerged through defective bone and at some point has torn, meaning CSF can now leak out. A further possibility is that there is herniated and torn dura from the beginning of the injury but that haematoma formation has previously prevented CSF from leaking out.

CSF rhinorrhoea of the spontaneous type is typically observed in adults, where its occurrence is linked to a normal elevation in ICP happening as a child becomes an adult. The CSF within the dural layer overlying the anterior cranial fossa can be at various pressures at any one time, as the arterial pressure changes, and in accordance with the respiratory cycle. Any action that mimics the Valsalva manoeuvre (e.g. clearing the nose or defaecation) can raise ICP, and if there are defects in the bone, the dura may be torn.

Lieberman et al. reported that cases of spontaneous CSF leakage were significantly correlated with having several defective areas within the basal skull present at the same time. This occurred in 18.2% of cases (i.e. 8 out of 44). These researchers proposed that such defects may actually result from raised intracranial tension [10].

20.5 Diagnosis

If a case features clear rhinorrhoea occurring unilaterally and in conjunction with general headache, CSF leakage should be suspected. Such individuals may also have a change in their mental state, convulsions, or meningitis. Thus, CSF leakage needs to be on the differential diagnosis to avoid diagnostic error [30–32]. If the discharge results from a CSF fistula, this will become apparent when the patient puts his or her head down and stays in the position for several minutes. If CSF leakage is occurring in conjunction with benign intracranial hypertension, examination of the fundi will reveal papilloedema in both eyes.

20.5.1 Physical Examination

Patients need to be completely examined physically, including rhinologically (not forgetting endoscopically), the ears, head, and neck, and a nervous system evaluation should be performed. An encephalocele or meningocele may be seen using the endoscope. In certain individuals, CSF leakage may be observed endoscopically when the Valsalva manoeuvre is performed or the jugular veins are constricted bilaterally (the Queckenstedt-Stookey test). In the majority of cases, especially where CSF leakage occurs intermittently, physical examination fails to resolve the diagnosis.

Individuals who have undergone a head injury may have a leak consisting of blood and CSF, which may cloud the diagnosis. If blood is mixed with CSF, dripping the discharge onto filter paper reveals separation of the two components, the so-called "ring", "double ring", or "halo" sign. However, this sign lacks specificity for CSF and may lead to an incorrect diagnosis [11]. Whilst single-sided nasal discharge offers a clue to the location of the lesion, bilateral discharge does not. Beware, however, that particular conditions may lead to rhinorrhoea on the contralateral side to the main lesion. Paradoxical lateralisation occurs when there is dislocation in the position of the median structures, which divide the nasal cavity in half, such as the crista galli or the vomer. This situation may mean that CSF emerges from the opposite nostril to the leak site. CSF rhinorrhoea is most often found in conjunction with meningitis or pneumocephalus (in 30% of patients, each) [6].

20.5.2 Laboratory Tests

20.5.2.1 Beta-2 Transferrin

Beta-2 transferrin immunofixation at present is the ideal way to test for CSF in nasal discharge [12, 13]. Beta-2 transferrin occurs naturally in CSF, perilymph, and the ocular vitreous humour. Perilymph production is extremely low, and the risk that vitreous humour mixes with any other fluid is minimal; thus beta-2 transferrin possesses high specificity for CSF. It has been reported the assay is 100% sensitive and 71% specific when used to detect CSF leakage [14].

20.5.2.2 Beta-Trace Protein [15]

Beta-trace protein (prostaglandin D synthase) is mainly manufactured by arachnoid cells, oligodendrocytes, and the choroid plexus, although it can also be detected in the testis, heart, and serum in human subjects. The levels are affected by kidney failure, multiple sclerosis, stroke, and some nervous system neoplasms. The test has been applied diagnostically in numerous trials and is 92% sensitive, but 100% specific. The test does not assist in identifying the side or location of the leak and may be difficult to perform on intermittent cases of CSF leakage.

20.5.3 Imaging Studies

20.5.3.1 Computed Tomography (CT) Scanning

To find out the location of the leak, nasal endoscopy under direct visualisation may occasionally be adequate, but mostly this is not the case, unless patients have previously undergone surgery on the nose or sinuses. Radiological investigations may be diagnostically valuable, using plain X-ray, computed tomography (CT) in the coronal plane, or magnetic resonance imaging (MRI). Although plain X-rays have limitations, they may help to confirm fractures or pneumocephalus in patients who are too ill to undergo any other form of investigation. CT imaging of the

paranasal sinuses utilising thin slices but no contrast agent is the typical first investigation. Gaps within the bones of the basal skull, an air-fluid level within the sinuses, and pneumocephalus may be sufficient grounds, when they match the history, to allow a plan for treatment to be made. Small areas of defective bone may be missed on CT, whilst volume averaging may lead to incorrect identification of lesions. On occasions, a defect may be seen on CT, but CSF leakage may be occurring from another site instead. CT does however have an advantage in evaluating the craniofacial bones and identifying calcification in the basal skull region [13].

20.5.3.2 Cisternography

Cisternography utilising a radioactive agent introduced intrathecally has now been in use for a long period and can identify a CSF fistula if the clinical picture is consistent with CSF nasal discharge, but CT and MRI have not identified the location of the leak. Cisternography is likely to be of use where the volume of CSF lost is low or only occurs sporadically. In the past, metrizamide was employed as contrast agent, but currently an aqueous solution of iodine-based agent is in use [16].

Magnetic resonance cisternography employs T2 weighting and fat suppression, coupled with reversing the image to visualise CSF [17]. If contrast agent is observed to pass through a defective bony area in the basal skull, CSF rhinorrhoea can be confidently diagnosed. Likewise, if contrast agent gathers in one of the paranasal sinuses, this is also consistent with the diagnosis. Nonetheless, different values for the sensitivity of the test have been reported, usually linked to the volume of CSF leakage. Because the procedure is invasive, exposes the patient to radiation, and allows only approximate pinpointing of the lesion, there are limits to its usefulness [18]. For CSF rhinorrhoea, cisternography has been reported as being 92% sensitive and 80% specific [19].

20.5.3.3 CT Cisternography [20]

CT cisternography involves introducing a contrast agent intrathecally to allow a greater chance of diagnosing the site of CSF leakage. Unlike non-contrast CT, a single study is generally sufficient. In the majority of cases where CSF is actively leaking into the nose, this test can identify the leak. On the other hand, if the leak only occurs sporadically, CT cisternography may incorrectly fail to identify a leak. An additional caveat is that defects affecting the cribriform plate or ethmoid sinus may also fail to show up by this technique [6].

20.5.3.4 Magnetic Resonance Imaging (MRI)

MRI offers an especial advantage in that it can highlight density differences between normal and neoplastic tissue, shown by variations in signal intensity. Additionally, MRI can demonstrate opacified soft tissue in the paranasal sinuses. MRI loses some of its definition in areas of the bone, such as the basal skull and the paranasal sinuses. Where there are numerous areas of defective bone at the base of the skull, MRI has the most diagnostic value in identifying meningoencephalocele alongside CSF nasal discharge, a situation which often occurs in this type of case [21].

20.5.3.5 MR Cisternography [22]

A principal advantage to performing MR cisternography is that there is no need for contrast material to be introduced intrathecally. T2 weighting of images allows for the identification of CSF within the nose, avoiding invasive procedures such as contrast injection. MRI can be set up to follow a pulse pattern such that there is a maximum chance of identifying CSF intranasally or in the sinuses. However, as occurs in CT cisternographic studies, if CSF leakage is only sporadic, the scan may miss CSF rhinorrhoea.

20.5.3.6 Intrathecal Fluorescein

Fluorescein may be introduced intrathecally and endoscopy (with or without the blue light) and then used to check for CSF leakage. The classic way to perform the procedure is to perform a lumbar puncture and then use the endoscope in the nasal cavity to look for a green liquid, indicative of a CSF leak. This procedure can provoke heart rhythmic disorders, convulsions, headache, and loss of function in the cranial nerves; hence the use of fluorescein intrathecally is outside the licence for the agent, meaning that the patient will need careful explanation before providing written consent to proceed [23]. On the plus side, it is documented that intrathecal fluorescein may be as much as 73.8% sensitive and 100% specific in identifying CSF leakage [24].

20.5.3.7 Nuclear Medicine Studies

Another possibility is to infiltrate a radiopharmaceutical into CSF via lumbar or suboccipital puncture. Repeated scans or obtaining a scintigram allows evaluation of where the radiopharmaceutical has become distributed.

A frequent addition to the procedure described above is to put pledgets at various points in the nose where leakage of CSF is most likely. The pledgets collect any radioactivity and can be analysed for its presence. There are several suitable radiopharmaceuticals, such as iodine-131, radioactive iodinated serum albumin (RISA), ytterbium-169, diethylenetriamine pentaacetic acid (DTPA), indium-111 DTPA, technetium-99 m human serum albumin, and ^{99m}Tc pertechnetate [6].

20.6 Treatment

When the source of CSF leakage has been established, the next things to consider in managing the condition are the likely cause, location, and amount of CSF actually leaking. If CSF flow is considerable, the leak is unlikely to stop without intervention, usually operative. By contrast, a CSF leak that involves little actual loss may resolve without surgery. This latter type may respond to conservative measures, such as enforced bed rest, keeping the head up, avoiding Valsalva-like movements, and inserting a lumbar drain to briefly divert the course of CSF circulation [25]. Given that most CSF leakage secondary to non-open head trauma gets better on its own, conservative approaches are reasonable except where neurological deficits develop or there is a further lesion within the skull that needs to be addressed [16].

If the problem does not resolve with a conservative approach, operative repair will be needed, whether an open craniotomy or endoscopically guided repair. Open repair may involve a bifrontal craniotomy, but if the cranium is not opened, an external ethmoidectomy or frontal sinusotomy is also possible. The open transcranial approach does, however, have the advantages that it lets the whole of the torn dura be seen at operation, gives access to deal with injured tissue around the area of leakage, and permits a vascularised pericranial flap to be employed to blanket the basal skull anteriorly [26]. The open transcranial approach, given these benefits, is a valuable choice if the CSF leakage is high-volume, occurring at several different points, involves raised ICP, keeps recurring, or cannot for any reason be adequately addressed endoscopically [24].

The open approach does, though, suffer from several associated risks, notably intracerebral haemorrhage, swelling of the brain, damage to the frontal lobe, lengthier hospitalisation, inability to smell, and a greater chance the same problem recurs, compared to repair performed endoscopically [27].

Endoscopic repairs are carried out via the nose using the rigid endoscope with linear or angled optics to permit viewing the roof of the nose and sinuses. There are a number of techniques and materials employed in endoscopically guided repair, amongst which autologous and non-autologous grafts, as well as tissue sealants, can be mentioned.

Grafts fulfil four roles: space-filling by providing bulk, ensuring water tightness, providing stiffness and support, and stabilising the periphery of an injury. Space-filling is achievable by use of adipose tissue, which can expand. A watertight layer can be provided with fascia, acellular dermis, rotated flaps, or grafts of mucosa—all of which are rich in collagen. Rigid support needs can be supplied by cartilage, bone, or a metal prosthesis. Cellulose, gelatin sponge, or tissue sealants can give stability in the periphery of an injury [28].

Some authors have argued for treating immediate CSF leakage via the nose following accidental injury by a conservative approach, since such cases tend often to resolve on their own. In such a situation, conservative treatment entails between 7 and 10 days confined to bed, with the bed-end kept at an angle of 15–30°.

There are a number of operations suitable for repairing defects in the base of the anterior skull. Intracranial repair used to be a common and routine technique and is still chosen in particular situations. The operations usually began with a frontal craniotomy.

If the posterior table of the frontal sinus is defective, this region can be accessed by marking an incision in a coronal direction and creating an osteoplastic flap, which then allows visualisation of the whole posterior table. This technique is particularly suited where the hole is higher than 2 cm above the floor and the lamina papyracea lies medial to it.

Endoscopic surgery is superior in several respects to external approaches. The surgical field may be easily seen since the endoscope can illuminate and magnify the view and offer views from different angles. Grafts (both overlay and underlay types) can be placed with greater accuracy when the endoscope is used. Indeed, it

has been repeatedly shown that endoscopic surgery achieves success in 90–95% of cases where a defect in the skull base is needed to be blocked off [29–34].

20.6.1 Conservative Management

Some authors have argued for treating immediate CSF leakage via the nose following accidental injury by a conservative approach, since such cases tend often to resolve on their own. In such a situation, conservative treatment entails between 7 and 10 days confined to bed, with the bed-end kept at an angle of 15–30°, which ensures a reduction in the pressure of the CSF within the basal cisterns. Patients need to be advised not to cough, sneeze, blow their nose, or lift heavy objects unless absolutely necessary. Prescription of stool softening agents will be of benefit in lowering the increase in intracranial pressure associated with defaecation.

It is also possible to drain off around 5–10 mL of CSF hourly by means of a subarachnoid lumbar drain. Draining steadily over time is better than sudden draining of fluid from time to time, since it avoids wide fluctuations in CSF pressure. This technique is not easily applicable if the bony defect causing the leak is extensive or where the damage has occurred iatrogenically. Since using the drainage technique potentially means the defect will persist, some clinicians are opposed to this way of treating CSF leaks [6].

20.6.1.1 Antibiotic Pharmacotherapy

Clinical logic dictates that a sterile space that is open to a non-sterile space will eventually become non-sterile, as occurs when the intracranial space is connected to the sinuses and nose. Accordingly, some clinicians use antibiotics on a prophylactic basis in those with CSF nasal leaks. There is, however, no firm evidence to support the practice as preventative of ascending meningitis.

Ratilal and colleagues published a literature review showing that evidence is lacking for any benefit from antimicrobials in cases of a fractured skull base, whether associated with CSF leakage or not. Five RCTs were compared in which cases of skull fracture were randomly allocated to antibiotics or placebo. These trials demonstrated that antibiotics offered no benefit in terms of preventing meningitis, reducing death from whatever cause and death from meningitis, and reducing operative interventions. The researchers did, however, point to a biased methodology in all the studies, concluding that the question of the usefulness of antibiotics on a prophylactic basis in patients with a fractured skull base remained unresolved [17].

20.6.2 Diuretics

Acetazolamide may offer adjunctive benefit in managing cases of spontaneous CSF nasal leakage linked to raised ICP. Acetazolamide is a sulfonamide which lacks

bacteria-killing properties but is an inhibitor of carbonic anhydrase, thereby preventing the formation of hydrogen and bicarbonate from carbon dioxide and water. It is thus mainly a diuretic.

This action then results in a lower concentration of H^+ ions within the epithelium, which inhibits the action of Na^+/K^+ ATPase, and thus less addition of water to CSF. The volume of CSF is therefore lower [6].

20.6.2.1 Surgical Therapy

There is a range of suitable operative techniques available to stop CSF leakage from the anterior basal skull. The advances made in the use of the endoscope within the last three decades have led to a shift in how surgeons view repair of this region.

In general, how successful a repair performed using the endoscope is does not depend on the type of graft used, especially when the defective area is below 2 mm in diameter. The technique of onlay grafting using mucosal or fascial tissue usually suffices if a defect is between 2 and 5 mm across. If the osseous tissue around the defect is fragmented, or the dura mater torn to a significant degree, composite grafting will be needed. Composite grafting generally entails the use of several layers, meaning both under- and overlay grafts are employed. Where the lesion exceeds 5 mm across, composite grafts are necessary.

The presence of raised ICP is another key element to consider, since defects secondary to raised ICP and of encephalocoeles necessitate the use of several layers of graft, whereas if ICP is within normal limits, selecting what material to use for grafting and how to apply it is less crucial.

There are a number of materials available to use as a graft. Alongside the size and position of the lesion and the key question of whether ICP is raised, the clinician's own choice and familiarity with the procedure and the availability of each graft type play a role in the final decision.

Underlay grafts are generally made of bone. Initially, a pocket is formed in the epidura, after which the graft is positioned with the dura on one side and the defect on the other. As long as there is sufficient material to overlap the margins of the defect, the graft should not move out of position.

The choice of donor site from which to obtain bone for grafting is wide. Since the bone of the septum is readily available to the endoscopist, this is a common harvesting site; however, where this is inadequate, a different site may be chosen, such as the calvarium, the iliac crest, or the tip of the mastoid. These latter sites necessitate an incision which can be seen externally and may be quite painful after surgery, particularly in the case of the iliac crest.

The grafted material is held in position by the application of fibrin glue, and an additional graft of adipose tissue, obtained in most cases from the patient's own abdomen by performing a paraumbilical incision at the beginning of the operation, may then provide extra sealing of the defect. A paraumbilical incision is preferable to an incision at a tangent on the lower right side of the abdomen, since not only does this give a better cosmetic outcome but also prevents the scar being mistaken for evidence of an appendicectomy [6].

20.6.2.2 Techniques for Reconstruction

Provided that CSF leakage is of low volume and the defect not overly large, repair can proceed using a non-vascularised graft. Where the defects are complicated, a mixture of vascularised and non-vascularised grafting methods may be employed [28].

There are several possible sources of material to use in inlay grafting, including fascia lata, decellularised dermis, and other artificial materials. Such graft types can be positioned inside the skull cavity and rest on the bony edges of the defect. For onlay grafting, the grafts are positioned on the outer surface of the basal skull, but extra materials will then be needed to reinforce the graft, and, because of this, onlay grafting is rarely used on its own, instead of being used where several layers are utilised to repair the defect. Medium-sized defects, out of which CSF is actively leaking, are frequently repaired by use of composite grafts. Composite grafts usually consist of inlay and onlay grafts, tissue sealants, and buttressing material. There are many ways to use a composite graft, including their use in conjunction with a pedicled flap providing a blood supply, a technique suitable for sizeable defects with large CSF leakage [28].

Cukurova and colleagues have published a description of their technique used to repair CSF leakage by suturing the dural layer, using the endoscope to provide vision [35]. This method depends on the dura being closed without being under tension; hence it is only suitable for the situation where there is a large defect in the bone, but minimal tearing of the dura. Laser tissue welding as part of endoscopic repair has demonstrated the ability to seal a leak more effectively than usual and without provoking an inflammatory response. This technique is still experimental [25].

The use of vascularised flaps has significantly strengthened the ability to carry out basal skull repairs endoscopically. Such flaps benefit from being well-supplied with blood in an axial direction and thus tend to survive for longer periods. Two types in use are nasoseptal and turbinate flaps. Free grafts from inside the nose have a less regular vascularisation, and this limits their use, especially when a large flap is required. Amongst the vascularised flaps most commonly used to patch basal skull defects, the nasoseptal flap deserves mention [19]. It benefits from being easily produced, having an extensive mucosal surface, being easily rotated to where needed, and possessing suitability for sellar, suprasellar, clival, and anterior basal skull defects. For these reasons, it has achieved popularity as a technique [19]. A potential area to harvest a flap can be evaluated by use of Doppler ultrasound [36]. Defects which occur centrally or posteriorly are suitable for reconstruction with an inferior turbinate flap, especially if the pedicle is sited posteriorly [37]. Inferior turbinate flaps receive blood from the posterior lateral nasal artery, which arises from the sphenopalatine artery. Extensive defects in the anterior fossa may be reconstructed using a vascularised flap formed from the lateral wall of the nose. These flaps utilise mucosa overlying the lower turbinate and the floor of the nose and have a pedicle sited in an anterior direction [38]. If the septum or lower turbinate cannot supply a flap, the middle turbinate may be used [39].

Potential drawbacks of using a flap include the flap undergoing necrosis or being dislodged and problems arising at the site of harvesting.

Tissue sealants can help to stabilised a graft with several layers used in reconstruction. Sealants may be non-natural chemicals or be based on a fibrinous matrix. It is unusual to employ an artificial material as the key component in a CSF leak repair [40]. Although tissue sealants of both types perform well, they suffer from high cost.

20.6.3 Anatomical Location Influences How CSF Fistulae Are Managed

Where in the basal skull region the leak occurs gives much information about how likely an operation will succeed [28]. The most frequently encountered leaks are as follows, cribriform plate, sphenoid sinus, anterior ethmoid sinus, frontal sinus, posterior ethmoid sinus, and inferior clivus, at a frequency of 35%, 26%, 18%, 10%, 9%, and 2%, respectively [36]. Defects in the ethmoid and sphenoid are suitable for repair using the endoscope, but leaks in the frontal sinus generally call for open-type repair [36]. The most likely repair to fail is one performed on the frontal sinus (44%). If the defect extends superiorly or laterally on the posterior table, success is less likely [41]. If the frontal recess is unusually narrow in the anterior-posterior direction, or the defect is too far in a lateral direction to reach with the endoscope, open repair will most likely be called for [41].

Surgery is complicated where the defect is located in the lateral recess of the sphenoid sinus. A defect on the extreme lateral aspect can be approached endoscopically by a transpterygoid approach. The pterygopalatine fossa is accessed by removal of the posterior face of the maxillary sinus. To reach the sphenoid sinus, the fossa must first have its contents removed [42].

Defects in the cribriform plate and the anterior ethmoid usually necessitate use of a graft of mucosa with overlying of bioabsorbable matter plus packing (not bioabsorbable) to bolster the repair [43]. The bony margin of the defect needs to be first exposed, including any mucosal covering, after which the graft can be put into place [28].

20.6.4 Intracranial Repair

In the past (and sometimes still), CSF leakage in the anterior cranial fossa has been routinely performed using an intracranial repair technique, usually involving frontal craniotomy. A middle fossa or posterior fossa craniotomy was also available if needed, but seldom employed. A variety of reconstructive methods have been employed, which encompass flaps of periosteum or dura mater, both free and with a pedicle, muscle plugs, sections of falx cerebri which have been rendered mobile, fascial grafting, and flaps bound with fibrin glue. An intracranial approach does not allow straightforward access to defects in the sphenoid sinus.

Intracranial repair benefits from being able to visualise the surrounding cerebral cortex, see any tears in the dura directly, and fix CSF leaks even where ICP is raised, by using bigger grafts. If it has proven impossible to localise the leak before surgery, intracranial repair can still prove effective, even without knowing the exact location of the leakage. For such a situation, repair grafts are applied all across the cribriform plate and the sphenoid.

Intracranial repairs do, however, suffer from drawbacks, such as greater morbidity, possibly permanent damage to the sense of smell, and iatrogenic injuries secondary to retracting the cerebrum, such as haematoma formation, impaired cognition, convulsions, brain swelling, and haemorrhage. Patients also need to remain in hospital for a longer period, which makes the operation more costly. Intracranial repair fails 40% of the time at first attempt, and the final failure rate is one in ten [6].

20.6.5 External Approaches

An external approach is suitable to access a leak affecting the posterior table of the frontal sinus. The operation involves making a coronal incision and utilising an osteoplastic flap, the latter allowing the complete posterior table of the frontal sinus to be seen and being particularly valuable where the defect is greater than 2 cm above the floor and laterally to the lamina papyracea. On occasion, a more straightforward approach is incising the eyebrow and using a trephine on the frontal sinus whilst also using the endoscope to perform an extensive frontal sinusotomy. This approach needs to be performed carefully, so that the frontal recess as a whole and the mucosal surfaces are not injured more than absolutely necessary.

20.6.6 External Ethmoidectomy

The first step in external ethmoidectomy is joining the eyelids together on the side of the leak as a protection against damaging the cornea. An incision as deep as the bone is performed, situated at the midpoint between the medial canthus and the nasal midline. The periosteum is lifted laterally, and this reveals the anterior lacrimal ridge and fossa. The lacrimal sac needs to be lifted away from the lacrimal fossa.

The periosteum is lifted backwards in the line of the lamina papyracea until the anterior ethmoid artery is met at a point between 2 and 2.5 cm to the rear of the lacrimal crest. Ligating this vessel means greater exposure can be obtained. Surgeons should avoid dissecting above the frontoethmoid suture, which is at the same level as the fovea ethmoidalis. The location of the posterior ethmoid artery is 1.2 cm behind the anterior ethmoid artery, following the frontoethmoid suture. The optic nerve is a further 5 mm posterior to that point.

20.6.7 Trans-ethmoidal Sphenoidotomy

Trans-ethmoidal sphenoidotomy commences in the same fashion as external ethmoidectomy (see preceding section). The ostial opening of the sphenoid sinus is

located and a small curette or beaded probe used to open up the ostium. Enlarging this hole is possible with a Kerrison punch. The sphenoidal anterior wall is very carefully taken away to allow access in the area of the sella [6].

20.6.8 Transseptal Sphenoidotomy

There are two ways to begin a transseptal sphenoidotomy—a sublabial and a translabial incision. Approaching via the sublabial incision means also performing a gingivobuccal sulcus incision which gives access to the pyriform opening and the spine of the nose. Identification of the caudal septal cartilage is then needed, before a septal mucoperichondrial flap (either unilateral or bilateral) is created and taken in a lateral and inferior direction following the floor of the nose and staying within the subperiosteal plane. The cartilaginous septum is separated from the maxillary crest, and a mucoperiosteal flap is lifted in the same fashion on the opposite side from the first flap. The contralateral nasal septum, as a result, is not detached from the cartilage. When the point of juncture of the bone and cartilage appears, the bone and cartilage are separated, and the posterior flap is raised on the opposite side. Removal of the bony septum leaves the sphenoid rostrum in view. The rostrum may then be taken away using an osteotome, and the whole of the sphenoid sinus is then visualised [6].

20.6.9 Transantral Approach

Approaching the basal skull via the antrum allows the anterior sphenoid, ethmoids, pterygopalatine fossa, and maxilla to be accessed more widely. The Caldwell-Luc procedure refers to radical antrostomy of the maxillary sinus. The anterior maxillary sinus wall is approached by means of a gingivobuccal sulcus incision. The periosteum is lifted upwards to the level of the infraorbital nerve, but this procedure requires meticulous attention so that the nerve is not damaged where it passes through the infraorbital foramen. Entry into the maxillary sinus is possible following osteotomy of the canine fossa. This access can be enlarged with a Kerrison rongeur. The ethmoid is reached superomedially via the maxilloethmoidal angle. Moving more posteriorly allows for exposure of the sphenoid sinus. If necessary, the pterygopalatine fossa may be exposed by opening the rear wall of the maxillary sinus [6].

20.6.10 Endoscopic Approaches

Use of the endoscope offers several benefits unavailable using open techniques, such as an improved view of the surgical field, thanks to superior lighting, magnification, and angled views. A further benefit is that grafts (both under- and overlay types) can be placed with greater precision. According to numerous studies, using the endoscope to repair defects in the basal skull succeeds in 90–95% of cases [29–34].

As noted above, endoscopic repair in CSF nasal leakage has several key benefits over open techniques. Yet another way in which endoscopic approaches are superior is in their ability to remove mucosal surfaces around the defect without a corresponding increase in the size of the defect. The precise placing of grafts is thanks to the ability to visualise directly. Endoscopic procedures are quicker and cause lower levels of morbidity. Thus endoscopic techniques are preferable in every case other than where there is another intracranial pathology to address, such as a mass lesion. Note that laboratory methods to detect CSF in nasal discharge do have a significant degree of false positivity [1].

20.6.11 Transfrontal Approach

The transfrontal approach makes the floor and rear wall of the frontal sinus accessible. In most cases, CSF leakage occurring here can be repaired transfrontally. It is essential that outflow from the sinus is not damaged in any way; otherwise a mucocele will eventually result. The key benefit to the technique is that the frontal sinus is not destroyed by creating an osteoplastic flap. If the defect is located at the extreme lateral or superior points of the frontal sinus, the endoscope may not be sufficient at present to perform a satisfactory repair.

The initial step in the procedure is total ethmoidectomy, after which the frontal recess is located and dissected. This region is made wider using the endoscopic adaptation of Lothrop or Draf III, thus giving a complete visualisation of the posterior wall of the frontal sinus [6].

20.6.12 Transcribriform Approach

This technique allows for exposure of the medial anterior cranial fossa, extending from the medial side of the middle turbinate as far as the olfactory sulcus. In a posterior direction, the exposed area goes as far as the anterior aspect of the jugum sphenoidale. Removal of the ethmoidal perpendicular plate makes the crista galli accessible. Dissection in the vicinity of the olfactory sulcus needs to be extremely cautious given the likelihood that any injury to the olfactory fibres may result in anosmia [6].

20.6.13 Transfoveal Approach

The lateral portion of the anterior cranial fossa is approachable via the fovea ethmoidalis. The area to be dissected is between the middle turbinate and as far as the lamina papyracea. Anteriorly the dissected area is bounded by the frontal sinus, whilst the anterior wall of the sphenoid sinus demarcates the posterior boundary. For certain cases, removal of the middle turbinate permits a combination of transfoveal and transcribriform techniques [6].

20.6.14 Transjugal Approach

The transjugal approach permits exposure of defects within the basal skull in the area of the jugum sphenoidale, as well as where the suprasellar area is significantly affected. Initially, anterior ethmoidectomy is carried out, after which a posterior ethmoidectomy is performed. The extreme anterior aspect of the planum sphenoidale is revealed by this technique. To give access in a posterior direction, the sellar anterior plate is removed.

20.6.15 Transsellar Approach [44]

Where defects are confined (at least mostly) to the sella, a transsellar approach is ideal. An initial total ethmoidectomy precedes identifying and opening the ostial entrance to the sphenoid. The ostia need to be considerably widened so that the sella is accessible as widely as possible. If access to the sella is necessary on both sides, this is possible through removal of the posterior bony septum and the intersinus septum.

20.6.16 Transclival Approach [45]

The transclival approach necessitates total ethmoidectomy on both sides and a wide sphenoidectomy. Both the intersinus septum and rostrum are removed. The area dissected is between the carotids laterally, and this area then includes the basal sella, the optic canal bilaterally, and the superior clivus. By making a hole in the rear wall of the sphenoid sinus, the most superior third of the clivus becomes accessible. Laterally, there should be no dissection beyond the sixth cranial nerve. Should it be necessary to reach the inferior two thirds of the clivus, exposure of the nasopharynx is achieved transnasally. The basopharyngeal fascia is incised, as are the prevertebral muscles. The surgeon drills into the clivus up to the point where there is exposure of the dura. The eustachian tubes indicate the position of the vertical segments of the carotid arteries and demarcate where the dissection should finish in a lateral direction.

20.6.17 Transpterygoid Approach

The transpterygoid approach starts with a medial maxillectomy adapted for the endoscopic technique. Maxillectomy allows the lateral limit of the maxilla to be seen widely, as well as the rear wall of the maxillary sinus. The position and route of the infraorbital nerve should be noted. The next stage is total sphenoethmoidectomy. Isolation of the crista ethmoidalis is followed by identification of the principal branch of the sphenopalatine artery.

At this stage, a decision needs to be taken about using a vascularised nasal-septal flap for repair of the leak. Use of a vascularised nasoseptal flap necessitates

preservation of the sphenopalatine artery and its more proximal supply. On the other hand, free mucosal grafts mean that this artery can be safely coagulated. Whether a vascularised flap is used or not, the bony posterior table of the maxillary sinus is taken away to allow dissection of the sphenopalatine artery in a proximal direction so as to find the internal maxillary artery and the branches (ascending and descending). Identifying the sphenopalatine artery is of further importance as it allows the position of the pterygopalatine ganglion to be known, since it lies immediately behind the vessel. This ganglion should not be damaged. Parasympathetic fibres originating from the ganglion are involved in tear production [6].

20.7 Factors Predicting a Successful Outcome in Endoscopic Surgery

There are multiple factors which affect the success rate in surgery for CSF rhinorrhoea. The research has highlighted how essential it is to differentiate between low- and high-flow CSF leakage at the stage when a treatment plan is being formulated [46].

The use of a vascularised graft is associated with greater success in repairing extensive defects in the dura than the use of free grafts [47]. The use of the endoscope to resect pituitary macroadenomas and clival chordomas also leads to greater success in closing the CSF leak than the sublabial approach using the microscope [48–50]. In contrast, endoscopic resection is less successful in the resection of craniopharyngiomas and meningiomas, which may well be due to their being located within the dura [50]. Using a nasoseptal flap for closure after dissection within the arachnoid space and tumour removal with the endoscope leads to fewer complications, especially when the surgeon has a higher level of experience [51]. Patients with hydrocephalus or benign ICP have more complicated outcomes. A study which looked at individuals undergoing repair of CSF leaks found that all the cases where the leak recurred were associated with hydrocephalus [26].

In cases of raised ICP, generally placing a lumbar drain to tap off excess CSF is advantageous during surgery. This takes some pressure off the dura, allows the defect to be raised, and thus permits a better siting of the graft. Certain experts recommend that lumber drainage remain in place for 24–48 hours after surgery [13]. This approach does, however, entail the risk of meningitis, pneumocephalus, and long-term headache, restricts patient movements, and may mean a longer stay in hospital. Thus each case should be assessed on its own merits. Where there are complex defects in the basal skull causing a high amount of CSF loss before and during surgery, consideration should be given to the use of a lumbar drain [52].

Following surgery, it is essential that the graft remains integral. Patients should be prohibited from actions that may damage the graft or raise ICP, such as lifting weighty objects, high-impact exercise, or other activities involving strain. There does not appear to be an association between the graft material used and how successful the operation is, as long as the CSF no longer leaks. It is for the surgeon to decide which graft to use, based on his/her familiarity with different approaches

[53]. Nonetheless, there is an association between autologous grafts and better quality of life post-surgically than is obtained with non-autologous types [54, 55].

20.8 Complications

The most serious and alarming consequence of CSF leaks is the potential for bacterial meningitis to occur, usually as a result of infection by *Streptococcus pneumoniae* or *Haemophilus influenzae*. There is a 10% risk of developing meningitis in the initial 3 weeks after skull base injury, but in cases of non-traumatic CSF leakage, this is as high as 40%.

There is some evidence indicating that non-surgical management (bed rest and CSF lumbar drainage) raises the risk of ascending infection. Some authorities therefore propose rapid progression to surgical intervention. There is a high risk of death occurring in cases of meningitis secondary to persistent CSF leakage.

Meningitis develops de novo after operative closure of CSF leaks in less than one in a hundred cases, and meningitis may not always be the result of bacterial infection. Indeed, in some cases, the meningitis develops as a result of the meninges having become irritated intra-operatively and is aseptic.

Whilst deaths occur at a rate of between 1 and 3% when an intracranial operation is undertaken, mortality from external approaches is close to zero. The main complication from intracranial approaches is the development of anosmia, found in between 20 and 25% of patients [6].

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Imaging of Cerebrospinal Fluid Rhinorrhea

21

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21.1 Introduction

Cerebrospinal fluid (CSF) rhinorrhea is defined as the leakage of CSF into the nose through an osteodural defect in the skull base, which leads to a fistula between the subarachnoid space and the sinonasal cavity [1]. Since this communication puts the patient at an increased risk of developing meningitis, surgical intervention is required for treatment of continuing CSF rhinorrhea [1, 2]. Accurate detection of the site of CSF leak facilitates appropriate treatment, helping to decrease the risk of life-threatening complications [1–4].

Recent improvements in imaging technology, particularly the introduction of multi-detector computed tomography (CT), have led to better delineation of skull base defects. Imaging is crucial in precise localization and detailed evaluation of the leak, as demonstration of the exact location, size, and contents of the osteodural defect leads to more accurate planning of surgery. Also, radiological identification of critical adjacent anatomical structures before surgery increases the rate of surgical success with less morbidity.

Another important task of imaging is determination of the cause of CSF leak. Clinical history, physical examination, and/or nasal endoscopy may be insufficient to reveal the etiology, which can be various, either traumatic or

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_21

non-traumatic, including underlying cephalocele, tumor, or disease such as idiopathic intracranial hypertension [1–5].

21.2 Clinical Considerations

21.2.1 Etiological Classification

21.2.1.1 Traumatic

The CSF leaks are classified according to their cause as traumatic or non-traumatic [1, 3–7]. Traumatic CSF leak constitutes approximately 80–90% of the cases and could either be accidental or iatrogenic [6–10]. Anterior and central skull base fractures are commonly associated with traumatic CSF leaks, with the cribriform plate, ethmoid roof, posterior wall of the frontal sinus, and the walls of the sphenoid sinus being the more frequent subsites [1, 4, 11–14] (Fig. 21.1).

Iatrogenic trauma due to skull base surgery is the cause of CSF leak in 16% of traumatic CSF rhinorrhea cases [15–18]. CSF rhinorrhea may be seen following endoscopic sinonasal surgery or transnasal endoscopic interventions involving the sella, clivus, foramen magnum, and craniovertebral junction. Potential hazardous sites during sinonasal surgery include the anterior ethmoid roof, particularly the cribriform plate and lateral lamella, posterior ethmoid roof, sphenoid sinus, and posterior frontal sinus wall [15–17] (Fig. 21.2). Hyperpneumatization of the sphenoid sinus and its extension particularly into the anterior clinoid process poses an additional risk during anterior clinoidectomy for paraclinoid aneurysm clipping [18].

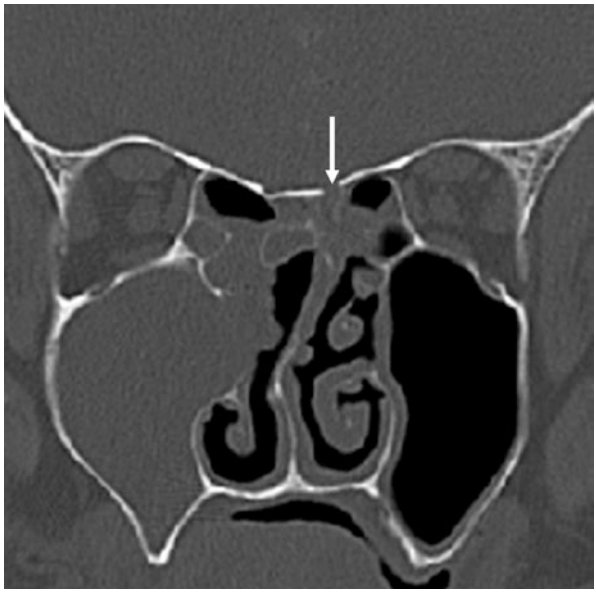

Fig. 21.1 Coronal CT reveals anterior skull base fracture and osseous defect (arrow) due to accidental trauma

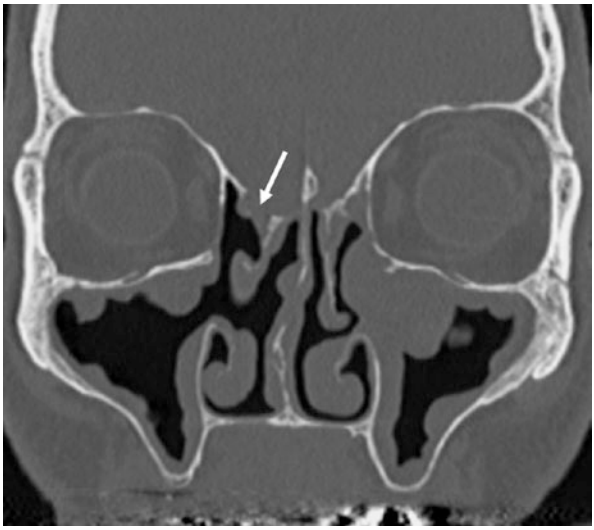

Fig. 21.2 Coronal CT reveals an osseous defect (arrow) in the right ethmoid roof in a patient presenting with CSF rhinorrhea following endoscopic sinus surgery

A persistent or delayed posttraumatic CSF leak increases the risk of meningitis, warranting a detailed imaging evaluation in order to define a specific location for surgical treatment [1–4, 7]. High-resolution computed tomography (HRCT) may reveal an osseous defect or fracture line of the skull base, and a fluid density (measuring between 0 and 10 HU) representing CSF within an adjacent sinus may be apparent. Intracranial air density next to a fracture line may also point to the location of the leak [7].Careful evaluation of the anterior ethmoid roof is required; particularly the insertion site of the vertical lamella of the middle turbinate is predisposed to iatrogenic injury. Before surgery, it is important to document any variant or dehiscent anatomy, particularly when there is an absence or distortion of important anatomical structures, such as middle turbinate resection secondary to a previous surgery. In a postoperative patient, a superior sinonasal soft tissue mass with an hourglass shape may be suggestive of a cephalocele [7]. Intraoperative image-guided navigation is useful in avoiding inadvertent injury of the skull base, especially in such difficult cases [19].

21.2.1.2 Non-traumatic

Non-traumatic causes, identified in approximately 3–4% of patients with CSF rhinorrhea, include congenital, neoplastic, or destructive inflammatory or granulomatous disorders and spontaneous fistulae [5, 20–25]. CSF leak has also been reported in patients following chemotherapy and/or radiation therapy for skull base tumors due to tumor shrinkage or osteoradionecrosis [24–27]. CSF leakage has also been described in noncommunicating hydrocephalus, where the increased intracranial pressure may result in ventricular decompression through a skull base defect [28].

Congenital lesions such as cephaloceles, giant arachnoid granulations, congenital osseous defects such as lateral craniopharyngeal canal, and ecchordosis physaliphora are implicated in CSF fistulae [3, 7, 23–25, 29, 30]. Congenital cephaloceles

may present with CSF rhinorrhea [7] (Fig. 21.3). When a bony defect in the skull base contains soft tissue density extending from the intracranial area into an adjacent paranasal sinus or nasal cavity is shown by HRCT, a magnetic resonance imaging (MRI) should be performed in order to evaluate for a possible cephalocele, which may be seen as a small cystic collection on MRI [4, 7, 20]. This CSF extension may contain meninges and neural and/or gliotic tissue [4].

Spontaneous CSF fistulae are leaks without any identifiable cause present and make 4% of all CSF leaks; however, the incidence has increased in more recent reports to 20.8–40% [3, 19–23]. They occur commonly in middle-aged obese females, and there is a strong association with cephaloceles and idiopathic intracranial hypertension [1, 3, 4]. Spontaneous CSF fistulae are mostly located at the cribriform plate, lateral lamella, ethmoid roof, and inferolateral or pterygoid recesses of the sphenoid sinus and in the perisellar region [1, 3, 30–33].

The mechanism for the occurrence of spontaneous CSF fistulae is attributed to increased intracranial pressure and aberrant extravenous arachnoid granulations causing erosion of the dura and the osseous skull base by continuous CSF pulsation [3, 7, 21, 32]. This condition may lead to osteodural defects and/or cephaloceles resulting in spontaneous CSF fistula, particularly adjacent to pneumatizated areas such as the inferolateral recess of the sphenoid sinus where a developmental bony defect, called the lateral craniopharyngeal canal (Sternberg's canal), may exist [3, 7, 21, 32, 33] (Fig. 21.4).

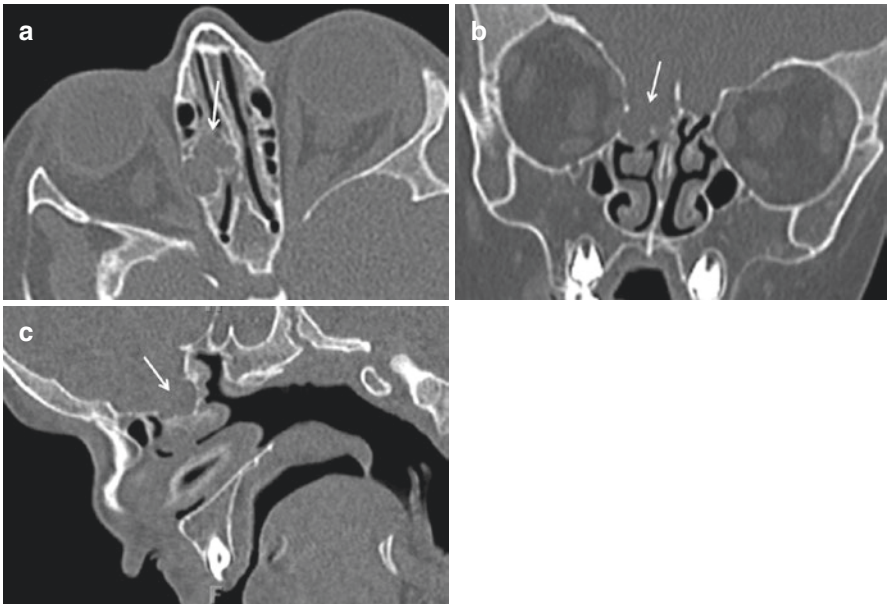

Fig. 21.3 Congenital ethmoid cephalocele: Axial CT image (**a**) shows an expanded and opacified ethmoid sinus with remodeling of the sinus walls. Coronal (**b**) and sagittal (**c**) reformatted CT images show an osseous defect of the skull base and extension of intracranial soft tissue density into the ethmoid sinus consistent with a cephalocele

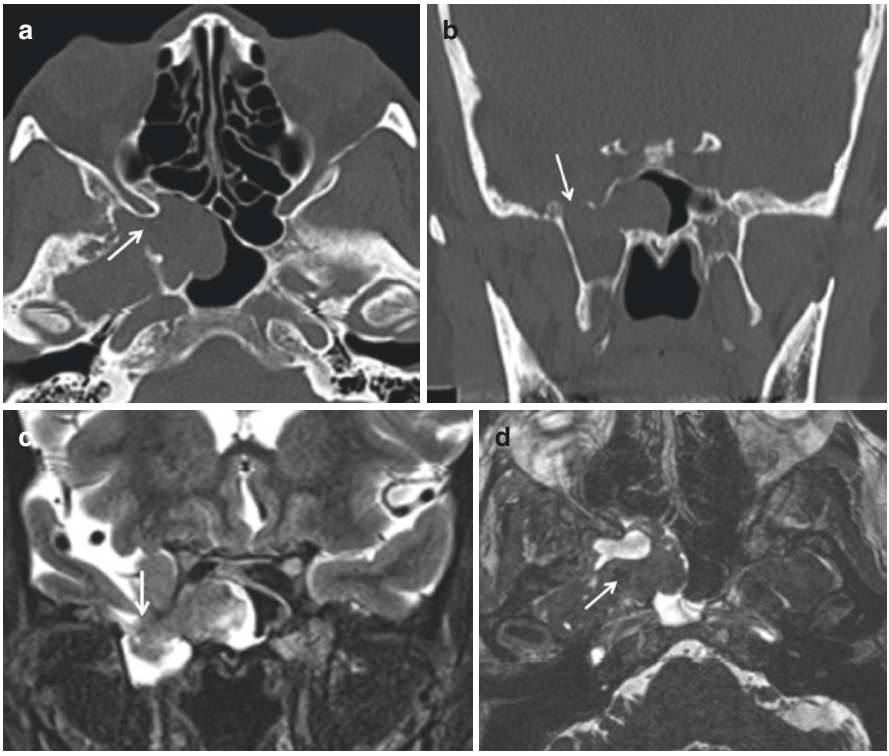

Fig. 21.4 Sphenoid sinus encephalocele: Axial (**a**) and coronal (**b**) CT images show a cephalocele extending into the sphenoid sinus through the osseous defect (arrow) in the roof of the lateral recess. On T2- weighted MR (**c**) and MR cisternogram (**d**) cerebral parenchma is revealed in the sphenoid sinus

The arachnoid granulations can be bilateral and multiple and can be differentiated from tumoral invasion by the characteristic CT appearance of smooth lobulated contours along the calvarial inner table or sinus wall with no mass effect [7, 20]. Other imaging findings associated with a CSF fistula include an accompanying cephalocele, scalloping of the calvarial inner table, empty sella, and petrous apex cephaloceles [7, 20, 21]. When intracranial hypertension is suspected, enlargement of the optic nerve sheath, posterior scleral flattening, prominent optic nerve head, stenosis of the transverse sinus, and low-lying cerebellar tonsils may be present on imaging studies, while definitive diagnosis requires documentation of elevated opening pressure on lumbar puncture [1, 3, 4] (Fig. 21.5). The intracranial pressure may be pseudonormalized in patients with active CSF fistulae; hence the suggestion of the diagnosis by the radiologist is important for appropriate medical and surgical management of IIH, because of the otherwise unfavorable prognosis and risk of recurrence at the same or a new location with skull base thinning or defect [3, 7, 20–22, 32].

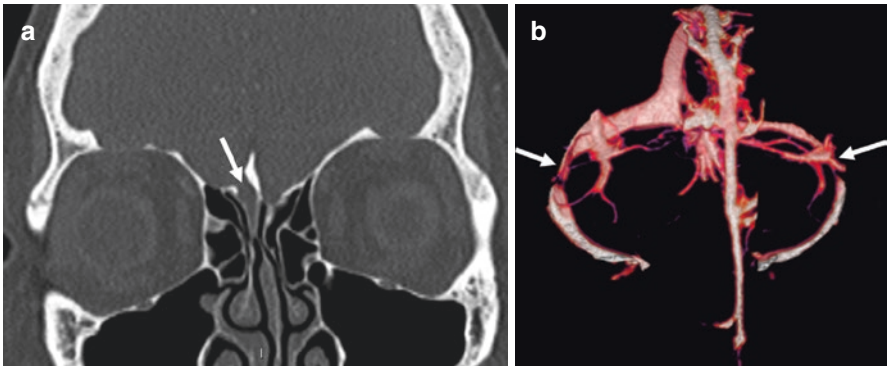

Fig. 21.5 Idiopathic intracranial hypertension: Coronal CT (**a**) shows an osseous defect in the cribriform plate in a patient with spontaneous CSF rhinorrhea. MR venogram reveals bilateral transvers sinus stenosis consistent with idiopathic intracranial hypertension. (**b**) MR venogram reveals bilateral transvers sinus stenosis consistent with idiopathic intracranial hypertension

21.2.2 Pre-imaging Work-Up

Pre-imaging work-up in patients with rhinorrhea includes nasal endoscopy and confirmation of CSF rhinorrhea with beta-2 transferrin test or beta-trace protein test.

21.2.2.1 Nasal Endoscopy

Nasal endoscopic examination in patients with CSF rhinorrhea is unlikely to identify the site of the leak since the findings are often nonspecific. In patients with an anterior cranial base meningocele or meningoencephalocele, the examiner can visualize a pulsatile nasal mass which may sometimes be difficult to differentiate from nasal polyps.

21.2.2.2 Beta-2 Transferrin Test or Beta-Trace Protein Test.

The most common biochemical method for confirmation of CSF leakage used to be glucose oxidase detection in nasal fluids; however, it is no longer recommended due to false-positive results in diabetic patients. Therefore, detection of other biomarkers of the CSF leakage, such as beta-2 transferrin and beta-trace protein, is necessary when collection of nasal fluid is feasible.

Beta-2 transferrin is a glycoprotein that is present in CSF, but not in nasal mucus, tears, or blood [34]. It can remain detectable for 14 days in all CSF samples, regardless of being stored at 4 °C or room temperature [35]. Multiple studies have shown high sensitivity and specificity of this noninvasive test [2].

Beta-trace protein is another marker that can be used for the detection of CSF. It is present in high concentrations in CSF, but in very low concentrations in blood. Although it has a 100% sensitivity and specificity, it cannot be reliably used in patients with bacterial meningitis and renal insufficiency [36]. Beta-trace protein test is a more rapid and less expensive test than beta-2 transferrin test; however, it has limited availability [2].

21.3 Diagnostic Imaging

Imaging is essential for CSF rhinorrhea to identify the exact site of the leak, to characterize the osteodural defect, to plan surgery, and to evaluate the underlying cause. Various modalities including HRCT, MRI, and cisternography techniques using CT/MRI or radionuclide scan are described and widely used; however, there is no single best modality [1, 2]. HRCT scanning of the skull base is the modality of choice for depicting the bone defects; however, evaluation of the adjacent soft tissues is best achieved by MRI, making these two cross-sectional tools complementary to each other [21, 37, 38]. HRCT images can also be used for intraoperative image-guided navigation [19].

21.3.1 Diagnostic Modalities

21.3.1.1 High-Resolution Computed Tomography

HRCT is the first line of imaging used to localize the site of the leak, in patients with clinically confirmed CSF rhinorrhea [1, 2, 39]. HRCT clearly delineates the sinonasal and skull base anatomy including the bones, as well as revealing bony defects that could possibly be associated with CSF leak. Whether the CSF leak is active or intermittent does not influence the detection of the osseous defect; therefore, CT is a good option in all patients with CSF rhinorrhea. The integrity of the bones of the skull base is examined, and skull base defects and fractures are identified by high-resolution imaging, using thin sections and bone algorithm. With the advent of multi-detector scanners, volumetric acquisition through the skull base can be obtained, and thin-section images (<1 mm) not only in axial plane but also coronal, sagittal, and oblique sections and three-dimensional images can be reconstructed as necessary [1, 6]. Appropriate evaluation of the dataset using optimum window settings at a dedicated monitor by an experienced radiologist is mandatory for documentation of subtle CSF fistulae or fractures [38]. In addition to localization of the CSF leak, the size of the defect can also be measured precisely by multi-detector CT [39].

The principal CT finding of a CSF fistula is an osseous defect, appearing as a disruption in the integrity of the continuous bone density in the skull base. The size and shape of the defect can vary widely. The posterior and lateral walls of the paranasal sinuses are usually evaluated in the axial plane, but the roof of the ethmoids and the sphenoid, particularly the cribriform plate, should be evaluated in multiplanar reformatted images, particularly on the coronal sections [1, 32, 33]. The presence of soft tissue adjacent to an osseous defect can be associated with CSF fistula [39] (Fig. 21.6). In a total or partially opacified sinus, a density measurement between 0 and 10 Hounsfield units (HU) confirms fluid content [1]. In patients with trauma, single or multiple linear defects may be present, and an intracranial air density next to a fracture line may be pointing to the location of the leak [7]. In addition to the sinonasal walls, the integrity of the temporal bone should also be inspected because CSF otorrhea may also drain into the nasal cavity through the Eustachian

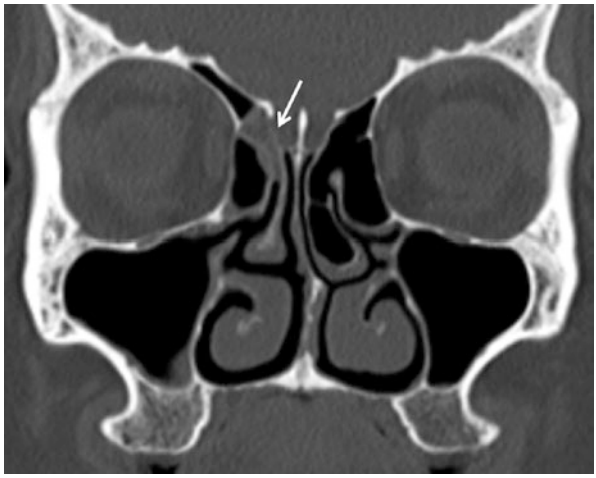

Fig. 21.6 Coronal CT shows an osseous defect (arrow) in the lateral lamella and adjacent soft tissue density in the right ethmoid sinus in a patient presenting with spontaneous CSF rhinorrhea

tube and the nasopharynx, presenting as CSF rhinorrhea [1, 3, 4]. In the setting of a destructive process such as tumor, infection, or granulomatous disease, additional imaging findings related to the primary lesion may also be evident.

Despite being very useful in demonstrating the bony detail of the skull base, CT may not be helpful in evaluation of the nonosseous structures. The depiction of any sinonasal opacification is straightforward; however, it is a nonspecific finding in CT, which may not only be due to CSF accumulation but also to inflammatory mucosal changes, polyps, secretions, or even a cephalocele [33, 37, 38, 41, 42]. Similarly, hematoma or fibrosis may also accompany skull base fractures in the setting of trauma and may be confused with CSF leak [43]. Particularly in the setting of an existing bone defect, the characterization of the associated soft tissue lesion is usually impractical. When a tumor or a cephalocele is suspected, further radiological evaluation with MRI is warranted [1, 38, 40]. The sensitivity and specificity of HRCT are variably reported as 44% to 100% and 45% to 100%, respectively [2, 37, 38]. The accuracy is reported between 87 and 93% [38, 44]. The sensitivity of HRCT was found to be over 80% in majority of these studies, and lower sensitivities were reported in specific patient populations such as those with inactive leak or postoperative patients. By the use of multi-detector CT, which is capable of obtaining thinner images at a higher resolution with multiplanar reconstructions, the diagnostic accuracy is likely to be increased [1, 39]. False-positive results may be caused by partial volume artifacts, vascular grooves, and normal variant defects which are not indeed the cause of CSF leak. It is important that scanning is performed in individuals with positive clinical findings, since small apparent bone defects may be seen normally [38, 40]. Use of thin-section and multiplanar images may reduce false-positive results; however, best results can be achieved by cisternographic methods that demonstrate the direct extracranial CSF continuity [38]. When multiple skull base fractures or a hairline fracture is present, the determination of the site of the active CSF leak may also be difficult, and hence demonstration of the active CSF fistula using cisternography techniques may be required to pinpoint the site of the active leak [1, 37–39, 43].

21.3.1.2 Magnetic Resonance Imaging and Magnetic Resonance Cisternography

MRI is the modality of choice for the evaluation of intracranial and extracranial nonosseous tissues. MRI is a noninvasive technique, with superior ability to characterize soft tissues in multiple planes even without the need for a contrast material injection. Whenever a skull base defect detected at CT is accompanied by an adjacent sinonasal opacity, the content of the opacified sinus should be further evaluated (Fig. 21.7). MRI is indicated to discriminate a possible cephalocele from other sinus lesions, such as inflammatory changes or high-density fluid accumulation as well as the evaluation of intracranial structures [1, 7, 21]. When there is clear extension of cerebral parenchyma or meninges through the defect, the diagnosis of a cephalocele is evident. However, herniation of intracranial contents may not always be obvious; indirect findings such as low-lying gyrus rectus (gyrus rectus sign), beak-like extension of the neural tissue owards the defect, associated mild encephalomalacia, and gliosis of the cerebral cortex may point to the diagnosis and are better appreciated on coronal T2-weighted fat-suppressed sequences [37, 38] (Fig. 21.8). Inflammatory sinus changes can be discriminated from CSF collection by significant hyperintensity of fluid on T2-weighted images, which is higher than the T2 signal intensity of inflammatory mucosal thickening. Inflammatory secretions may be of similar signal intensity to CSF accumulation on T2-weighted series; however if protein content of the secretions is high, then the presence of high T1 signal intensity may be helpful for discrimination of secretory fluid from the relatively lower T1 signal intensity of CSF [38]. Occasionally, the CSF fistula itself can be shown as a linear high-intensity fluid signal extending extracranially through the skull base [1]. Post-contrast T1-weighted fat-suppressed images in three planes may reveal accompanying reactive dural enhancement.

Magnetic resonance cisternography (MRC) is also a useful technique for evaluation of CSF leaks and can be obtained noninvasively on a 1.5 T or higher scanner, without the need for an intrathecal injection of gadolinium [1, 3, 4]. This technique depends on thin-section heavily T2-weighted imaging using balanced steady-state free precession sequences, where fluid signal is significantly bright in contrast to other structures such as bones or neural tissues appearing significantly dark. The advantages of this technique are high spatial resolution, high image contrast between the CSF and neighboring structures, high signal-to-noise ratio, multiplanar capability, lack of ionizing radiation, lack of need for intrathecal contrast material injection, and diminished bony artifacts. Images can be obtained in three planes and also can be reformatted in oblique planes if three-dimensional sequences are used [1, 45]. MRC can be combined with whole-brain routine cranial MRI sequences in order to rule out other pathology such as cephaloceles or intracranial and/or skull base tumors. MRC can localize CSF fistulae accurately and particularly may be useful in patients with a suspicion of cephaloceles or with multiple fractures or osseous defects [1, 2]. The appearance of a high signal intensity communication between the intracranial CSF and the extracranial paranasal cavities passing through the skull base represents a CSF fistula (Fig. 21.9). MRC is particularly more advantageous in patients with intermittent or slow leaks as the technique unlike CT cisternography

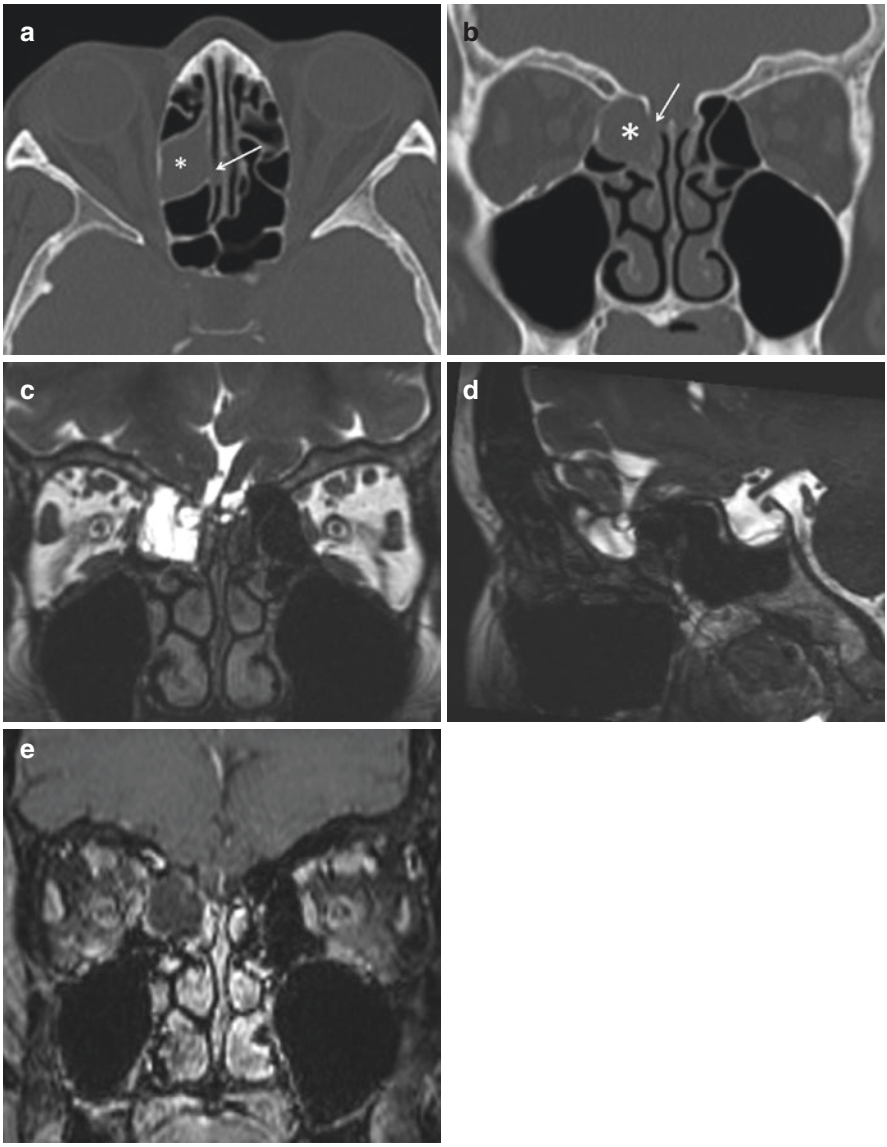

Fig. 21.7 Congenital cephalocele: Axial (**a**) and coronal (**b**) CT show a small osseous defect in the lateral lamella (arrow) and an adjacent opacified sinus (asterix). Coronal (**c**) and sagittal (**d**) T2-weighted images reveal a cephalocele extending through the defect into the ethmoid sinus and thin strands of gliotic tissue within the sac. Contrast enhanced T1-weighted image (**e**) shows no enhancement of the cephalocele

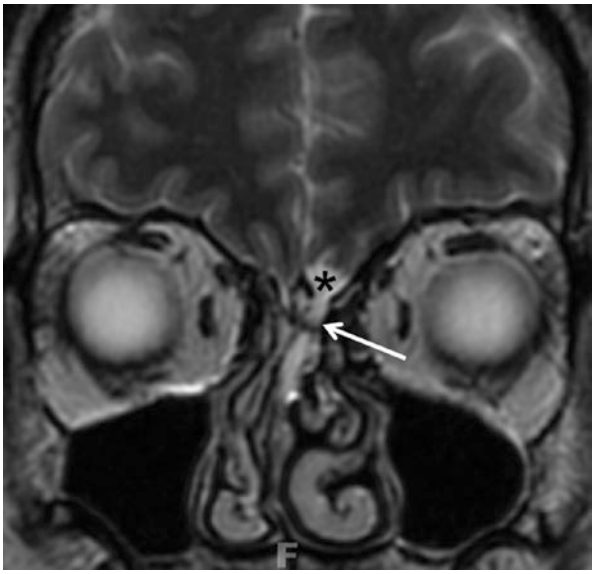

Fig. 21.8 Coronal T2-weighted MR image shows a small meningocele (arrow) extending into the left nasal cavity through the cribriform plate. Accompanying encephalomalacia of the adjacent neural parenchyma is also noted (asterix)

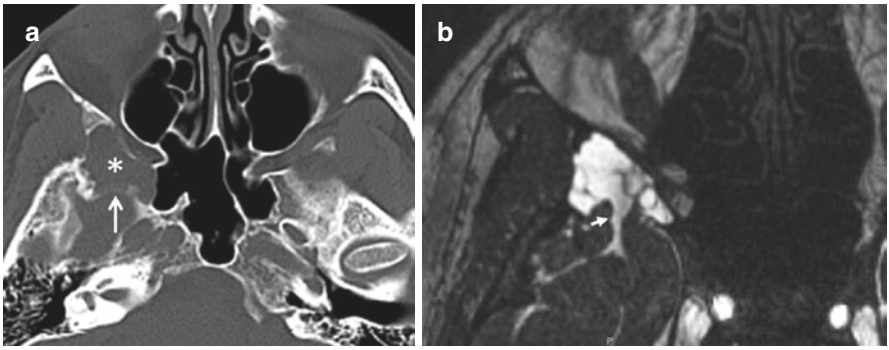

Fig. 21.9 Axial CT image (**a**) shows a soft tissue density within the right sphenoid bone (asterix). There is irregularity and thinning in the posterior contour of the sphenoid bone (arrow). Axial MR cisternogram (**b**) clearly demonstrates a high signal intensity extension of the intracranial CSF into the sphenoid (small arrow)

and radionuclide cisternography does not require the CSF leak be active during scanning [38, 41].

The sensitivity and specificity of MRC are reported to be 56–94% and 57–100%, respectively [2, 12, 21, 37, 38, 41–51]. The overall accuracy is between 78 and 96% [2, 20, 38, 43, 44, 48].

The disadvantage of MRC is the lack of bony detail [1]. Since osseous anatomy is better demonstrated by CT, MRC may be complementary for patients with CSF leak and osseous defect detected by CT [37, 38] (Fig. 21.9). The combined accuracy of HRCT and MRC is reported to be ranging between 92 and 100% [37, 38, 42].

Contrast-enhanced MR cisternography, which requires intrathecal injection of gadolinium-based contrast material, has been successfully implemented in multiple series reported, notwithstanding the concerns about CNS toxicity associated with gadolinium [11–13, 46, 47]. This technique, which is not FDA approved in the USA, is not recommended for routine use due to its invasive nature, the success of noncontrast MRC, and increasing concerns about gadolinium deposition in certain CNS sites [2, 11].

21.3.1.3 Computed Tomography Cisternography

Contrast-enhanced computed tomography cisternography (CTC) is considered to be the standard of reference for the radiological evaluation of CSF leaks [1, 40, 48, 52–58]. It confirms the existence and identifies the anatomical location of the CSF leak precisely (Fig. 21.10). However, this invasive technique carries inherent risks, such as headache or infection, due to lumbar puncture and

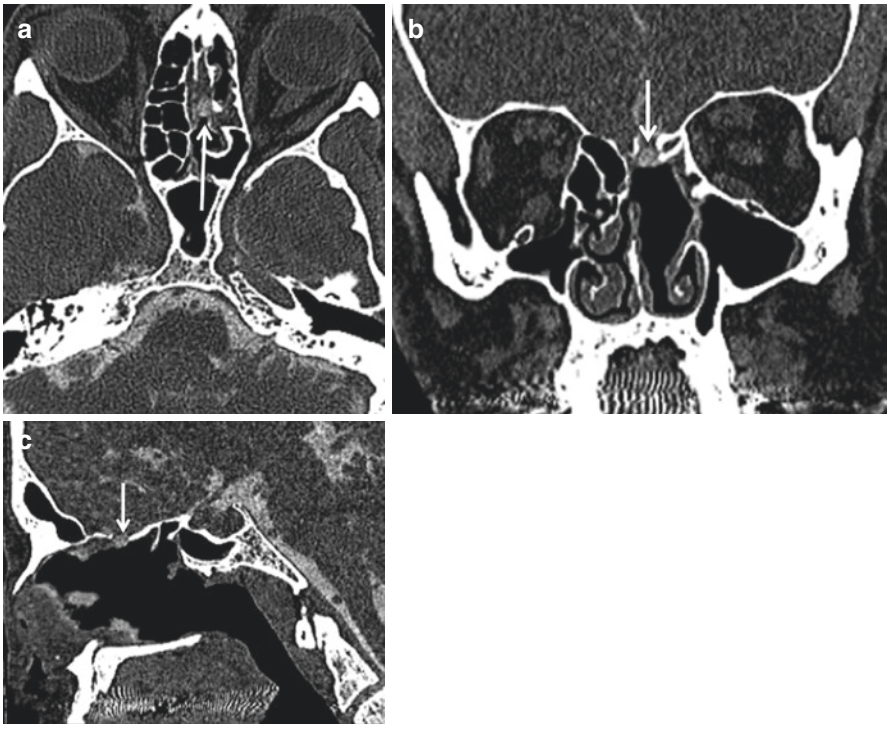

Fig. 21.10 Axial (**a**), coronal (**b**) and sagittal (**c**) CT cisternogram images show passage of contrast enhanced CSF (arrow) into the nasal cavity through an osseous defect in the cribriform plate in a patient presenting with CSF rhinorrhea following intranasal surgery

intrathecal injection of the contrast material, and is contraindicated in the setting of active meningitis or increased intracranial pressure [2, 52–58].

For CTC, thin-section HRCT images of the skull base are obtained before and after injection of iodinated contrast material in the CSF. The passage of contrast material into the sinonasal cavity is significant for a CSF fistula. Provocative maneuvers, such as prone position or sneezing, before post-contrast scanning may promote the leakage of the contrast-enhanced CSF. Pre-contrast images are useful to discriminate other high-density sinus contents, such as dehydrated secretions or blood [1] (Fig. 21.11). The accumulation of the contrast material within a sinus can be documented by Hounsfield unit (HU) measurements demonstrating a 50% or greater increase in density between pre- and post-contrast images [1, 40]. The most important limitation to this technique is its requirement for an active CSF leakage during the exam. For patients with intermittent or inactive leaks, modified techniques involving delayed scanning or high-pressure cisternography techniques have been described [1]. Occasionally, non-diagnostic scans occur due to inadequate contrast opacification in the basilar cisterns which may be related to poor technique, lack of patient cooperation, and unfavorable spinal anatomy limiting passage of contrast material from the lumbar spine to the intracranial space.

The sensitivity of the contrast-enhanced CTC is reported between 33 and 100%, and the specificity is 94% [2, 37–40, 44, 49, 52–58]. The accuracy of the method is between 33 and 63% [2, 20, 44]. The sensitivity is reported to increase to 80–92% with the use of low osmolar contrast material and in active leaks [1, 21, 23, 38, 40]. Since the diagnosis of an osseous defect can already be made with noncontrast HRCT, contrast-enhanced CT cisternography is reserved for patients with no visible skull base defect at HRCT or with multiple bone defects to determine the actively leaking one [38, 40].

21.3.1.4 Radionuclide Cisternography

Radionuclide cisternography is another method using intrathecal injection of radiotracer, most commonly diethylenetriaminepentaacetic acid (DTPA) tagged with

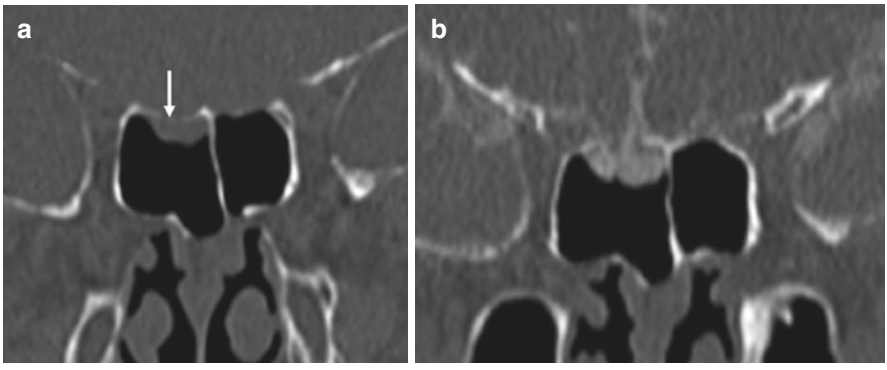

Fig. 21.11 Coronal CT (**a**) shows bone defect (arrow) in the right sphenoid roof and adjacent hypodensity within the sphenoid sinus. CT cisternogram (**b**) reveals the leak of contrast enhanced CSF into the sphenoid sinus

technetium-99 m or indium-111 [1, 22, 40, 59, 60]. Following injection, scintigraphic images of the head, including the sinonasal area, are obtained in Trendelenburg position in anterior and lateral projections [1]. The collection of the tracer in the sinonasal cavity or nasopharynx suggests CSF leakage; however this technique may not reveal CSF leaks that are inactive during the study. In complex cases, delayed imaging technique can be employed involving endoscopic placement of nasal pledgets before intrathecal injection of indium-111 (In-111) DTPA, with a longer half-life of 2.8 days [1, 40, 60]. The pledgets are removed 24–72 h later, and their radioactivity count is compared to that of the serum. A 1.5- to three-fold increase in pledget radiotracer ratio is considered positive for CSF leak. Pledget technique is particularly useful to confirm the presence of intermittent or slow-flow CSF leaks that cannot be revealed by other imaging methods; however precise localization is not possible although some localizing information may be gained from the location of the pledget in the nasal cavity [40].

The sensitivity of radionuclide cisternography is reported to be between 76% and 100%, while the specificity and the accuracy are reported as 100% and 90%, respectively [2, 22, 40, 44, 59, 60]. The sensitivity of the delayed pledget technique is reported to be 76% [40]. Radionuclide cisternography is not used routinely. It is mostly reserved to document the presence of the CSF leak in patients with an uncertain diagnosis [1].

21.4 Image Interpretation and Diagnostic Algorithm

When a patient presents with rhinorrhea, a detailed clinical examination, including history of a possible trauma or surgery, should be carried out. It is useful to evaluate the nasal fluid for presence of beta-2 transferrin in doubtful cases of CSF leakage, particularly prior to imaging [1, 2]. The initial imaging of choice for localization of the CSF fistula is HRCT of the skull base, including the temporal bones. Multidetector CT with thin-section images, less than 1 mm in thickness, can reveal most defects [1, 2, 44]. A detailed examination of the skull base by a dedicated radiologist at a workstation is required to reveal the osseous defect optimally; in addition to axial, coronal, and sagittal planes, images can be reconstructed in oblique planes as necessary, and dynamic adjustments of settings can be made. The most common sites of CSF leakage are the cribriform plate, fovea ethmoidalis, and lateral lamella [1, 3]. These are the thinnest structures of the skull base, and at times, it may be difficult to distinguish a defect from normal thinning. Therefore accompanying signs, such as asymmetric osseous thickness, adjacent soft tissue or fluid density, and deviation of crista galli, could point to CSF fistula [1]. These sites are followed by the sphenoid and frontal sinuses [38, 43]. Particularly in patients presenting with spontaneous CSF rhinorrhea, the inferolateral recess of the sphenoid sinus and the perisellar region should be carefully evaluated. Tegmen tympani should also be included in the examination, since temporal bone CSF leaks present with rhinorrhea when the tympanic membrane is intact. Radiological report should include the precise location and size of the defect. The defect size, as measured at HRCT, correlates well with the size of the defect found at surgery [39].

Noncontrast MRC is recommended as the second-line tool following beta-2 transferrin testing and HRCT when either one of these tests is not available or the results are inconclusive [2, 44]. MRC is useful for both confirming and localizing the CSF leak. MRI is helpful in characterizing the contents of an opacified area within the sinonasal cavity. Additionally, when HRCT demonstrates multiple osseous defects of the skull base, MRC may reveal the site of active CSF leakage. Thus, a combination of HRCT and MRC for evaluation of CSF rhinorrhea is generally preferred, since the two modalities provide complementary information to each other. The combined accuracy is reported to be ranging from 92% to 100% [7, 8, 42]. Superimposition of HRCT and MRC has also been recommended for successful localization of the active CSF leaks [37]. The sensitivity of the superimposition technique was 89%, and the correspondence between the fused images and contrast-enhanced CT cisternography was 100% [37]. HRCT and MRC are also useful for following up patients who have had surgery for CSF fistula.

Contrast-enhanced CT cisternography is useful in selected cases with persisting CSF rhinorrhea despite negative or controversial HRCT or MR cisternography studies (Fig. 21.12); however inactive intermittent leaks may not be demonstrated. Nuclear cisternography or CT cisternography with pledgets is recommended for complex cases, when no leak is demonstrable otherwise [1, 2].

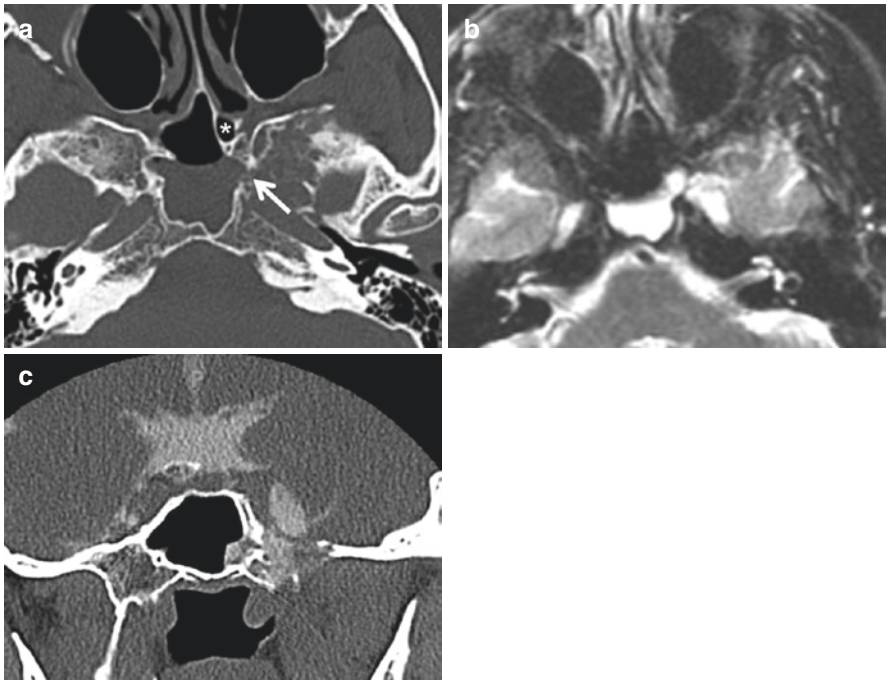

Fig. 21.12 Axial CT (**a**) and T2-weighted MR (**b**) images show irregularity and thinning of the lateral sphenoid sinus wall (arrow), air-fluid level in the right sphenoid sinus and a hypoplastic left sphenoid sinus (asterix). Coronal CT cisternogram (**c**) demonstrates the accumulation of contrast enhanced CSF in the sphenoid sinus

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Who Really Needs a Rhinoplasty?

22

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22.1 Introduction

Although rhinoplasty is a common operation, few surgeons can be considered expert in every technical aspect of the procedure [1, 2]. Rhinoplasty is said to be an operation that is straightforward to perform once, but very hard to perform constantly at the level of true excellence [1]. Over the last few decades, rhinoplasty has evolved from a simple reduction operation to a sophisticated combination of reduction, relocation, and augmentation, aiming to address various issues [3]. Many different ways to perform rhinoplasty are advocated by influential surgeons [4]. The plethora of different methods currently on offer can lead to confusion and concern about performing rhinoplasty, not only among new beginners but even among experienced practitioners. As everyone agrees, "noses are difficult to predict" [5, 6].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_22

22.2 Indications and General Concepts

22.2.1 Motivation

Even if the indication for rhinoplasty is to do with nasal function, the patient undergoing rhinoplasty usually still considers cosmetic aspects. Why patients agree to put themselves in discomfort, accept the risk, and shoulder the cost of a procedure, the main aim of which is an improvement in physical appearance, remains poorly understood. In the majority of cases, there is no direct correlation between the willingness to have the procedure and objective measures of nasal deformity. Likewise, psychometric measurements bear little relationship to how deformed the patient's appearance really is [7]. For those cases where cosmetic considerations predominate, the degree of distress is greater than in those having the procedure solely to improve nasal function [8]. Patients' satisfaction after rhinoplasty undertaken to address both functional and cosmetic needs depends more on aesthetic result than on improvement in function [9]. Since patients undergoing rhinoplasty are often preoccupied with deformities that others would neither notice nor be concerned about, it shows clearly that this group has already undergone alterations in the way they think. Candidates for rhinoplasty are unhappy with their looks than those contemplating other cosmetic procedures [10], and each time they look in the mirror, they recall their dissatisfaction, a situation which has generally already begun at the age of puberty [11, 12]. In 80% of cases, the motivating factor is a wish for an alteration in facial appearance or the experience of seeing someone else benefit from rhinoplasty [12, 13]. A move toward procuring rhinoplasty is generally taken as the patient gets older or if the individual becomes a "highly motivated doer" wishing to improve his or her facial appearance [14–16]. Surgeons and surgical candidates share the common goals of obtaining a more pleasing appearance, which brings higher self-esteem; decreasing anxiety in social situations; reducing obsessional preoccupation, aggressive behaviour, and persecutory thoughts; and thus providing for a better overall quality of life [8, 10, 17–21]. Such benefits are directly attributable to rhinoplasty itself, rather than some other factor, and self-esteem continues growing following the procedure [19]. In one sense, therefore, rhinoplasty may be viewed as a psychotherapeutic intervention [22].

22.2.2 Rhinoplasty and Body Image

In early work on rhinoplasty, which focused on psychoanalysis [23, 24], being unhappy with one's looks was seen as an outward manifestation of internal psychic conflict [9]. Candidates for the operation were deemed obsessional and to be displaying narcissism; hence psychiatric rather than surgical treatment was seen as more appropriate. Subsequent research, focused on clinical interviews, concluded that most candidates had some perturbation in their psychology, either a personality disorder or obsessional or neurotic disorders [17, 18, 25, 26]. Other researchers have objected to these findings as irrelevant to clinical practice [27, 28]. It used to be asserted that having a mental disorder should be a contraindication to rhinoplasty as the risk of being dissatisfied following the operation was too acute [29, 30]. Such

an opinion was not, however, evidence-based, and, indeed, the satisfaction rate following surgery, even among those with mental disorders, was above 80% [31].

22.2.3 Body Image Disorder and Dysmorphophobia

A distorted view of one's own physical appearance that leads to distress is termed body dysmorphic disorder, the most extreme form of which is dysmorphophobia [32]. Disturbance of body image occurs in between 7 and 10% of candidates for cosmetic surgery [32]. Body image disorders usually become apparent in adolescence, so cosmetic surgeons need to be keenly aware of the problem when a young person is requesting cosmetic surgery. The most common reasons for dissatisfaction with body appearance are acne and alopecia and then nasal appearance. It has been calculated that probably 26–40% of sufferers from body dysmorphic disorder actually succeed in undergoing a particular cosmetic operation [32]. However, only 3.6% of such cases result in improvement, and 25% of patients are subjectively satisfied with their final appearance. Surgeons may be able to identify potential body image disorder sufferers by asking themselves the following questions [32]:

1. Is the patient preoccupied by a defect in his/her appearance to an extent that seems unwarranted from the clinician's viewpoint?
2. Is this preoccupation causing distress that appears real?
3. Is there no other mental issue which could better explain the preoccupation, e.g. anorexia nervosa?

If the answers to these screening questions are affirmative, it is probable that the patient has a severe degree of body image distortion. A single affirmative response may be enough to raise suspicion of a distorted body image, and some authorities recommend not offering a cosmetic procedure [33], although others disagree [32].

22.3 Indications and Contraindications for Rhinoplasty

A surgeon with experience should be able to perform rhinoplasty either endonasally or by an external approach. Which approach is used depends on the rationale for performing rhinoplasty [34].

22.3.1 Closed Rhinoplasty

22.3.1.1 Indications for closed rhinoplasty

Closed rhinoplasty is indicated when:

1. There is a cosmetic defect.
2. The patient wishes to change his/her nasal profile.
3. There is an anatomical restriction on nasal airflow [35].

22.3.1.2 Contraindications

There are far more elective rhinoplasties than the other types. Since the surgery is elective, it is the surgeon's responsibility to be judicious in accepting suitable candidates for the procedure. Such a selection of suitable candidates relies on surgical considerations, the psychology of the candidate, and the dictum primum non nocere ("first, do no harm") to otherwise healthy people. The following are frequently occurring reasons why the operation should not be undertaken [35]:

- The patient's mental status is not stable currently (e.g. untreated schizophrenia).
- The patient has too high expectation from the procedure.
- Rhinoplasty (major procedure) has taken place already within the previous 9–12 months.
- The anaesthetic risks are unacceptable.
- Rhinoplasty has already been attempted multiple times, causing atrophy of the skin or soft tissues and marked scar formation.
- Misuse of cocaine by snorting.

22.3.2 Open Rhinoplasty

The following are all *indications for open rhinoplasty* [36]:

- To modify the tip of the nose.
- To rectify abnormal function of the nasal valve inside the nose.
- Where skin covering the nose is thicker than usual.
- To remedy a perforated septum.
- The candidate for surgery has a particular (non-white) ethnicity.
- The nose is deformed following injury and the septum or dorsum twisted to one side.
- The nose requires a high degree of augmentation, and tip, columellar, and spreader plus/minus shield grafts will be placed.
- The nose is deformed by a cleft lip and palate.
- To excise a malignancy of the nose.
- To act as a training opportunity.
- Secondary rhinoplasty [37, 38].
- Where the thin nature of the overlying skin means sculpting is of particular importance.

22.3.2.1 Contraindications for Open Rhinoplasty [36]

- Intranasal drug misuse (e.g. cocaine).
- Psychological or psychiatric instability.
- Features of the SIMON (single, immature, male, overly expectant, narcissistic) type of personality.
- Comorbidities that predispose to an unacceptable anaesthetic risk.

- The working diagnosis is dysfunction of the nose (+/− a cosmetic problem) for which closed surgery (in other words, septoplasty to alleviate airflow restriction) or pharmacological therapy is better suited.
- The surgical candidate will not accept a visible scar.
- The skin of the nose is very thick, and thus there is a risk that swelling following rhinoplasty will not resolve.

22.4 Non-surgical Rhinoplasty

The term non-surgical rhinoplasty is preferentially used for non-surgical aesthetic improvement with injectable fillers and toxins, whereas the term rhinoplasty is reserved for surgical nasal reshaping. Due to their reversibility, high G′ HA fillers are considered the safest material for non-surgical rhinoplasty. It is advisable that non-surgical rhinoplasty is performed only by highly experienced injectors with an intimate knowledge of injection anatomy and appropriate techniques that are of critical importance as the rich vascular network of the nose renders it a high risk area for severe complications [39–41].

22.4.1 Indications

– All dorsal and nasal base defects.

22.4.2 Contraindications

– Previous nasal surgeries with scarring.
– Previous injection of permanent and semi-permanent fillers into the nose.
– Insertion of alloplastic materials into the nose.

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Which Approach Should Be Applied in Rhinoplasty: Open or Endonasal?

23

Serkan Çayır, Cemal Cingi, and Norman Pastorek

23.1 Introduction

Endonasal rhinoplasty is a closed-type surgical approach, whereby any incisions are placed in the interior of the nose. Even though the surgeon still incises almost 50% of the interior nostril, the closed approach means that no scar will be seen from the outside of the nose. This is an advantage of this approach. Some open rhinoplasty defenders say that it comes at the cost of the limited visibility afforded by highly constricted operative openings, which renders the operation arduous, and putting the nasal skin back in place is challenging, but this is not true. The incisions on each side are disconnected. In addition, endonasal rhinoplasty has the advantage of keeping some natural attachments in their position, so it will be easier and safer to finalise the surgical procedure. As they claim that it is necessary to greatly stretch the skin of the nose to get to the framework supporting the nose and the surgeon inevitably distorts the nasal cartilage, this is not true. A closed rhinoplasty essentially means any procedure whereby the endonasal route renders less exposure than the open approach but still sufficient to allow the surgery to proceed [1].

In contrast, open (i.e. external) rhinoplasty employs an incision across the columella (i.e. transcolumellar) that joins the incisions made on both sides. Although this means an incision about 4–5 mm long will be visible externally, it does allow

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_23

the skin to be folded backwards along the longitudinal axis of the nose. This is somewhat akin to opening a car bonnet to show the engine. The lower nasal framework can then be visualised in its entirety. Open rhinoplasty is thus characterised by better operative exposure achieved by having the transcolumellar incision but having the risk of visibility of skin scar at the middle of the face [1].

Whilst closed rhinoplasty does allow the correction of multiple cosmetic nasal defects and, furthermore, avoids scarring of the columella, open rhinoplasty is more effective than the endonasal approach in highly deformed and asymmetric noses. The risk of a highly visible columellar scar is, in any case, only slight. Some practitioners have acquired great expertise in the endonasal approach, with good outcomes, especially where the nasal anatomy is uncomplex. However, where the underlying nasal problem is complicated, such as rhinoplasty in cleft lip, nasal torsion or grave post-surgical deformity, open techniques come into their own. Indeed, the majority of surgeons with expertise in rhinoplasty see endonasal rhinoplasty as the first choice. The open procedure may be the preferred approach in extremely difficult asymmetric noses or teaching purposes [1].

23.2 Aetiology

The indications for rhinoplasty may be classified as either congenital or acquired, as follows [1]:

Congenital conditions encompass [1]:

- Deformity of the nose secondary to orofacial cleft.
- Congenital anatomical deformity.
- Familial or ethnic.

Acquired conditions encompass [1]:

- Deformity caused by injury:
  - Broken nose.
  - Fracture of nasoorbitoethmoidal type.
  - Haematoma affecting the septum.
  - Bite injury.
  - Burn injury.
- Infective (such as *Treponema pallidum*).
- Neoplasia.
- Rhinitis (both allergic and vasomotor).
- Exposure to toxic chemicals (such as snorting cocaine).
- Disorders involving inflammation.
  - Connective tissue conditions.
  - Autoimmune conditions.

23.3 Assessment before Surgery

For surgery to be planned in an appropriate way, photographs need to be obtained before surgery, being obtained under standard conditions of technique, lighting and the views obtained [2, 3]. The views needed to allow surgery to be planned and the results evaluated are frontal, oblique, lateral and basal. Contemporary software applications are an excellent aid to teaching patients, planning before surgery and showing what can be reasonably expected. Although often referred to as "mock surgery", patients should be made aware that the image is a guide to what it is hoped to achieve, rather than a definitive guarantee of success [3, 4]. If used cautiously, computerised visualisation lets both patients and clinicians ensure they understand the same thing about what the operation is aiming to achieve, something difficult to manage in words alone [5].

23.4 Endonasal (Closed) Rhinoplasty

Rhinoplasty refers to a range of surgical procedures that aim to change how the nose functions and/or appears [6]. To achieve operative access, the nose may be incised inside the nose alone (i.e. endonasal approach) or accompanied by an external incision, typically transcolumellar. Before the open rhinoplasty became more favoured amongst surgeons in the last 10 years or so, virtually all rhinoplasties were endonasal in type. Although the distinction between what constitutes an open and a closed rhinoplasty is not greatly significant, since the incisions in both cases are typically in the same locations, and the techniques have much else in common, the terms "open" and "endonasal" have become accepted as integral to describing the methods available to achieve rhinoplasty [7].

There are a number of reasons for a deformity of the nose to occur, which are as follows [7]:

1. Genetic (familial), e.g. hump deformity of the dorsum.
2. Injury (e.g. post-RTA).
3. Iatrogenic (especially an unsatisfactory outcome from prior surgery).
4. Congenital, such as secondary to cleft palate.

Those who favour a closed approach in rhinoplasty cite the following as reasons to prefer the technique [7]:

- There is less necessity for operative dissection.
- The procedure is less likely to result in weakening the support of the tip of the nose.
- A reduction in post-surgical oedema.
- A reduced risk of scar formation or the occurrence of iatrogenic injury.

- Even quite complex alterations are possible without moving the structures involved.
- Alterations to the nasal profile can be predicted and palpated more directly.
- Specific alterations are possible without dissecting the entire nose.
- The procedure is quicker than an open rhinoplasty.
- In theory, patients (notably elderly ones) should recover more quickly.
- There is no risk of external scarring affecting the columella.
- Post-surgical swelling is less.
- Normal appearance is restored in a shorter period than with the open approach.

23.5 Open Rhinoplasty

Currently, the open technique is amongst the most favoured and versatile of rhinoplasty methods. Since the procedure necessitates precise siting of the incision on the caudal margin of the lower lateral cartilage, being well-acquainted with nasal anatomy is a prerequisite. In practical terms, there is no absolutely definite way to define where the margin of the cartilage will be situated, even though the anatomy of the lower lateral cartilages [8–18] and the alar lobule [19] has been investigated in a number of studies. As a result, the operation must proceed stepwise, with dissection uncovering the margin of the cartilage. For the method to develop further, there needs to be a way to locate the inferior margin of the cartilage by reference to some anatomical landmark of known position [20].

The open method involves a short incision across the columella to connect with the nostrils, followed by further incisions endonasally, whereas incisions occur solely within the nose in the closed method [21].

A comprehensive patient account, including details of the difficulties in function or the degree of cosmetic dissatisfaction, is part of the clinical workup. Key topics to cover are symptoms and how long they have been present, any previous interventions undertaken, allergic history, substance misuse, drug history and full medical history. The reasons why the patient is seeking rhinoplasty must be carefully noted. For men, the personality features of the SIMON (single, immature, male, overly expectant, narcissistic) syndrome need to be assessed at this consultation [21].

Examination covers the external features of the nose, encompassing evaluation of the superior, middle and inferior thirds. In particular, the overall composition, the external nasal angles and the nature of the osseous and other tissues need to be recorded. The internal nasal examination will check the septum, the valves (both internal and external), the conchae and the lining mucosae. The tip of the nose and the dorsum should also be assessed in terms of form and structure. If needed, the examination may include the Cottle manoeuvre, mirror test and procedures involving vasoconstriction [21].

Our own view is that the entire rhinoplasty procedure should be photographically documented, before, during and after surgery. Such a record helps both the patient and the clinician. We take views from the front, side, below and above and to achieve a three-quarter profile [21].

Surgery may be remedial in several different conditions, such as:

1. Disorders affecting both the nasal exterior and cavity.
2. Cosmetic dissatisfaction.
3. Iatrogenic deformity secondary to previous rhinoplasty.
4. Blockage of the airway.
5. Congenital defect of the nose [2].

Open rhinoplasty offers the following benefits:

1. The bony and cartilaginous frameworks are directly exposed and may be easily inspected and assessed.
2. Defects may be remedied in an exact fashion and stability preserved (tip or dorsal alterations, graft positioning and osteotomy).
3. The procedure is very helpful for surgical training [22, 23].

On the other hand, external rhinoplasty does have certain drawbacks, as follows:

1. There may be scarring on the columella, and columellar flaps may necrose.
2. There is considerable removal of the skin from the bony and cartilaginous nasal skeleton, and this dissection technique may cause scar formation.
3. The procedure lasts longer than the endonasal technique.
4. The tip may undergo oedema and become numb post-surgically [21].

23.6 Open vs. Endonasal Rhinoplasty

Cosmetic surgeons have yet to reach consensus on the optimal technique to achieve rhinoplasty. Both open and closed procedures have much to recommend them. On the whole, however, open rhinoplasty is preferable in any case which has any degree of complexity. Thus the classic endonasal rhinoplasty is most suitable for cases which need a nasal hump to be removed and where a quicker operation with less oedema and potential for visible scarring is sought [24].

Surgeons usually adopt techniques with which they have become familiar during training or as a result of professional experience. As is often the situation, preference for one technique over another typically comes about through a combination of experience, the end being sought and how difficult an operation actually is [26].

The literature on open vs. closed rhinoplasty is extensive [22, 23, 25, 27, 28]. The undoubted advantages of the endonasal technique (no external scarring, reduced need to dissect and lower degree of consequent oedema, plus shorter time to perform) need to be set against the need for a more experienced practitioner, one who can cope with not being able to visualise much of the underlying nasal structures. The closed approach is less often indicated than an open approach but is useful for correcting a single defect in the tip of the nose or on the dorsal surface [29].

Open rhinoplasty is the more frequently performed procedure and is preferable in several respects, notably for allowing the nasal structures to be clearly visualised in an undistorted way, allowing a more exact analysis of the problem and a more targeted response [30–32]. This aspect of open rhinoplasty (greater exposure) gives the procedure value in postgraduate surgical training. The structures and the remedial procedures are both readily seen by a trainee. The drawbacks include oedema that resolves more slowly, longer operative duration, commonly the necessity to give extra support to the cartilaginous nasal skeleton and a visible transcolumellar scar [30, 32]. Such scars do, however, tend not to be very visible and thus seldom provoke problems [5, 33, 34].

If a case for rhinoplasty has no particular complications, such as only small changes, closed rhinoplasty may be more effective and suitable. Even if there are a number of issues to address, provided the nasal anatomy is symmetrical overall and does not deviate, the closed technique would still be an option. But if the case is complex, such as following earlier trauma, where asymmetry predominates and a notable deviation or congenital defects are present, open rhinoplasty is likely to be more suitable, since this technique gives greater surgical control over the resulting structural changes. A great deal of the literature on the topic mirrors these conclusions [26, 35–37].

The key aspect to consider in forming an opinion on the superiority of one technique over another is how a clear preference may be detrimental to surgical training. An instructor who is overly partisan on behalf of the open or closed approach may not be able to give the full picture. Surgeons undertaking cosmetic procedures on the face should really know both techniques. Only by being familiar with all the options will a clinician be able to recommend in an objective way the best approach to adopt, based on the features of a case and the aims in mind. A bias founded on limited training should definitely be avoided [26, 38].

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Selfies and the Rising Demand for Rhinoplasty

24

Mehmet Emrah Ceylan and Can Cemal Cingi

24.1 Introduction

The sudden increase in the number of smartphones in circulation has brought with it a craze for selfie-taking. Selfies, a form of self-portraiture, are the stock-in-trade of social media platforms such as Instagram, Snapchat and Facebook. To an ever greater extent, the selfie is becoming a mirror in which individuals see themselves and judge supposed flaws in their own appearance [1]. Between 2016 and 2017, the proportion of cosmetic facial surgeons who had been consulted by individuals driven by a desire to improve their own appearance in selfies rose from 13 to 55% [2].

Selfies are ubiquitous, both in real life and on social media. It is probable that most people have taken their own selfie at some point. It is thought that typical individuals from the millennial generation will perform more than 25,000 selfies over the course of their lives [3].

Thus, "selfie culture" is becoming more predominant on a daily basis and across the entire world. Given the widespread notoriety selfie culture has acquired, it is natural that academics have begun investigating the basis of such a widespread phenomenon. Two topics, in particular, have garnered considerable attention amongst social investigators: what is driving this rise in the posting of selfies on social media and which individuals are the ones who post the greatest number of such images [4]?

Hall [5], writing for *The Daily Telegraph* in 2013, noted that young people were increasingly choosing to take a selfie rather than allow a photographer to capture their image. Maintaining a photographic record of family life was becoming less popular in younger people, being replaced by selfie creation and online posting in albums. One reason for such a change might be that a photograph is no longer

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_24

primarily seen as a snapshot memory. Indeed, Belk [6] has argued that photography has a capacity to communicate and create the identity of individuals on social media platforms. Social media and smartphones have facilitated communication greatly [7]. Digital assets can be archived and retrieved readily from both computers and smartphones [8]. A service aiming to provide users with extra online space for selfies, "Google photos", surprisingly received approximately 24 billion selfie images within a period of only 1 year [9].

Svelander and Wiberg [10], in an article entitled "Practice of selfies", suggest that a precise appreciation of the phenomenon of selfie-taking needs to encompass more than just the concept of the selfie as an amateur photographic record or as an indication of self-absorption and narcissism by the taker. They propose that, far from being a straightforward self-image capture, the selfie involves an interplay of factors relating the individual, the image, the social media and the smartphone. Selfie-posting also encompasses additional activities such as looking at selfies taken by different individuals; acquiring one's own image; selection, photo-editing and polishing of the selfie before choosing to make the image available to others; and anticipation of how others will react to the posting [4].

The selfie, aka photographic self-portraiture, has, in a short period of time, become a significant photographic genre in its own right. In a single year, 2014, Android devices were used to obtain 93 billion selfies [11, 12]. Selfie photography, whilst easy to accomplish, does in fact result in a distorted facial rendering, owing to the angle of the photograph. The most evident result of the technique is that the nose appears larger than it really is [13] (Fig. 24.1).

Fig. 24.1 Selfie of the editor (CC)

24.2 The Selfie

A selfie may be defined as a photographic auto-portrait, generally accomplished by means of a smartphone or webcam and often posted on a social media platform for others to see [14, 15]. Selfie-taking has risen in popularity recently, particularly with younger people. A survey on selfies revealed that, amongst adults aged 18–24 years, 98% had taken a selfie at some point, with 46% having done so on the day of the survey [16]. The peak age for individuals to take selfies is the third decade of life. Individuals at this stage in their life take and share selfies more frequently than either adolescents or older individuals [17]. Despite a growing body of knowledge about the sociopsychological characteristics of those who take and share selfies on social media [18–21], how selfies are actually perceived is less well understood. Indeed, paradoxically, selfies seem mainly to be negatively evaluated, despite the enthusiasm to take them. Re et al. [22] provide empirical data to back up this scholarly impression. These researchers were interested in how perceptions about selfies differed between the subjects portrayed and others who viewed them. They noted, incidentally, that auto-portraits attracted a higher level of negative evaluation than conventional photographs of the same individual. Since the study only noted this as an incidental finding, however, more narrowly focused research will be needed if the possible causes of such a finding are to be explained. The fact that selfies are so regularly negatively assessed would be expected to go against the willingness of individuals to take selfies. A study by Pounders et al. [23] revealed that individuals taking selfies want to appear more happy or to have a more attractive appearance, so as to project greater positivity in their self-image (Fig. 24.2).

Social media may be driving dissatisfaction with external appearance, the more so since almost all young adults use social media and often take selfies. In comparison, self-compassion has been cited as a potentially beneficial factor in preventing dissatisfaction with external appearance. One study looked at two issues: (1) how the degree to which an image was altered before posting (the psychological "investment" in hearing others' evaluations and dissatisfaction with external appearance were interrelated) and (2) the extent to which self-compassion affected the correlation between social media variables and being unhappy with external appearance. The subjects were 89 Australian men and 95 Australian women. The conclusion was that altering an image before posting and being highly invested in others' evaluations correlated with being more unhappy about one's looks, for both men and women. Alteration of selfie images before posting and worry about others' responses are potential risk factors for becoming dissatisfied with external appearance in both males and females [24].

24.3 Picture: Selfies Analysed from a Photographic Perspective

Selfie-taking may have a particular association with mobile devices and social media, but it is still, in essence, a photographic genre. In the light of this, the analytical tools used in the theory of photography (index, composition and reflexivity) are applicable to analysing selfies, too [25, 26].

Fig. 24.2 Postoperative selfie of a patent

Nonetheless, the selfie does not generally aspire to be a work of art, albeit that is sometimes the taker's intention. Rather, it is a snapshot of an informal kind. Snapshots are the most usual type of photographic creation. They are capable of aesthetic as well as social purpose [27]. The selfie is a picture that can achieve communication by means of gesture. A selfie may be read as an act of the subject with the message "see me showing you me" [25].

24.4 The History of the Selfie

Jim Krause, a photographer, was the first to use the term "selfie", which he did in 2005 [28]. Earlier examples of selfies can be identified. Facebook achieved dominance amongst various social media platforms in the early 2000s, when autoportraiture was a frequent feature of MySpace profiles. Kate Losse notes that "an amateurish flash-blinded self-portrait, often taken in front of a bathroom mirror" was viewed by many of those adopting Facebook as an indicator of poor taste, in the period 2006–2009. At this period, Facebook users generally opted for a more formal and better composed picture, taken by another person standing some way away. The expression "selfie" was employed in 2009 by a website offering image or video

hosting in reference to the apparently inexhaustible numbers of auto-portraits then being uploaded by adolescent females [29]. Losse credits technological advances in smartphones, such as the iPhone 4 (from 2010), which had a front-facing camera, and the introduction of image editing software applications to smartphones (especially Instagram and Snapchat) with bringing the selfie genre to the forefront in the early 2010s [30–32].

24.5 Selfies and Rhinoplasty

If a camera takes an image of the face from very close-up (e.g. around 30 cm away), the nose area appears to be 30% increased in size in comparison with the remaining facial features. This effect is attributable to perspective. Appearances alter according to the observer's distance from an object. Thus, a building when viewed close-up will appear larger than other buildings of the same size but situated further away from the observer. But with the observer situated at a significant distance (e.g. a kilometre away), the buildings will all appear the same size [1].

Placing a camera lens in close proximity to a face therefore produces a similar distortion in the image produced. Since the nose projects closer towards the camera, it will appear proportionally larger. Likewise, as the lens moves away from the face, the relative proportions move towards a closer approximation to reality [1].

Taking a photograph close to the face makes the width of the nose appear to occupy an increased proportion of the total facial width. The actual three-dimensional nasal appearance is thus misrepresented by the image. It has not yet been established whether the taking of selfies on a very frequent basis has any effect on the level of satisfaction post-rhinoplasty and, if so, how this translates into clinical decisions taken. There is a need for more modelling of the situation, taking into account the vertical height and horizontal position of the lens when a selfie is taken [13].

The American Academy of Facial Plastic and Reconstructive Surgeons reports that, following a survey, 42% of surgeons say they have encountered individuals whose motivation for aesthetic operations was to be able to take more attractive-looking selfies and other images to use on social media [33].

It is common for individuals seeking rhinoplasty to attend with selfies, on which they point out where they believe their appearance could be better. This is especially so amongst patients between 16 and 36 years of age. A few patients are actually able to find the most flattering photographic angle, but many have to distort the face to achieve their desired appearance [34]. It is common for patients seeking rhinoplasty to have an asymmetric face. This asymmetry was an unpleasant surprise to many such individuals in the past. This is often no longer the case, and many younger individuals have awareness of their features being asymmetrical. Prior to the popularity of selfies, most individuals would express dissatisfaction due to a humped nasal dorsum. Since these patterns are changing, it seems likely that selfies have intensified patients' scrutiny of their own facial features, and this scrutiny leads to dissatisfaction and a demand for rhinoplasty [32] (Fig. 24.3).

Fig. 24.3 Preoperative selfie of a patient

The principal male aesthetic concerns are for the elimination of rhytides and avoiding baldness, whilst women generally seek to appear younger by requesting a facelift and eyelift, with a pleasantly proportioned nose to match. The most frequently performed cosmetic interventions are Botox injections to counter rhytides, hyaluronic acid filler placement, hair transplant and rhinoplasty [35]. For women, facelift and rhinoplasty are the most usual, followed by dermal resurfacing by ablation and eyelid surgery. The number of procedures of each type performed was 37, 37, 36 and 34, respectively, according to one survey. A 2013 study [35] identified Botox for rhytides as the most frequent intervention (348 instances) and then filler injection (187 instances), superficial peels/microdermabrasions (119 instances) and resurfacing without ablation (106 instances).

Despite the popularity of such non-operative procedures, rhinoplasty ("nose job") continues to be the most frequently requested operation in both men and women under the age of 35, being sought by 90% of males and 86% of females [35].

The goals of aesthetic rhinoplasty include the following:

- Alteration in nasal dimensions.
- Correction of defective anatomy.
- Restoration of balance to the facial features and a more pleasant appearance overall.
- Improving the tip of the nose.
- Reducing a hump in the nose.

Whilst it is possible to achieve major improvements, candidates for surgery must be informed about how much can reasonably be expected and what the inherent limits of rhinoplasty are. Rhinoplasty cannot remedy self-esteem problems nor give an individual an ideal nose. Provided patient expectations are not excessive, an experienced surgeon performing rhinoplasty can expect most patients to be satisfied with the outcome [36].

To conclude, selfies have become more popular in tandem with the rise of the smartphone. The selfie is especially popular amongst young adults as an image to post on social media platforms. Taking a selfie is, however, not confined to any

particular age group or sociodemographic class. This development has occurred in the context of a greater public preoccupation with external appearance. Studies report increasing feelings of self-consciousness and awareness of the importance of personal attractiveness both socially and at work [37]. The role of social media in how an individual is perceived, for good or ill, is well-established, notably amongst adolescents [38]. Facebook and Twitter have been revolutionary in this respect [38].

Rhinoplasty, despite its technical challenges, has enjoyed a long period of popularity. The ability to customise rhinoplasty to an individual's requirements has not diminished the complexity, but has meant greater flexibility of approach. The contemporary increases in the demand for rhinoplasty are attributed by many practitioners to the increased scrutiny on people's appearance as a result of the selfie and social media usage. Given the trend for social media to exert ever greater influence, it is perhaps unsurprising to find that rhinoplasty and other cosmetic procedures and the selfie are associated with each other [32, 36].

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Assessment of Angulation Deformities of Lower Lateral Cartilages and Their Restoration

25

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25.1 Introduction

It has been said that "he who masters the nasal tip, masters rhinoplasty." This is true, because restoration of the nasal tip can be considered as the most difficult part of a rhinoplasty.

25.2 Clinically Oriented Anatomy of the Alar Cartilages

The shape of the tip is formed mainly by the lower lateral cartilages. Each of the lower lateral cartilage has its unique anatomy with several natural convexities, concavities, and angulations. These cartilages are thoroughly supported by attachments, namely, the intercartilaginous ligaments between the upper and lower lateral cartilages, sesamoid fibromuscular tissue between the lateral crus and pyriform aperture, interdomal loose connective tissue among the medial cruras and caudal septum, intercrural ligaments, and Pitanguy's ligaments [1, 2]. Lower lateral cartilages can be divided into three cruras (medial, middle, and lateral), each composed of two segments divided with distinct junction lines. Medial crus is divided into columellar and footplate segments. Middle crus is divided into domal and lobular segments. Lateral crus may be subdivided into the lateral crus and the accessory cartilage ring. The junction between the medial and middle crura is called columella-lobular

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_25

junction. The junction between the lobular and domal segment matches with the medial genu. The junction between the middle crura and the lateral crura is called domal junction and matches with the lateral genu [3].

Tip restoration may become more complicated with several deformities existing over the lower lateral cartilages. One of the most challenging of these deformities is the presence of inappropriate, abnormal, and resistant angulations over several parts of the lower lateral cartilages. Most of these angulation deformities are located over junction lines between segments and cruras. They can exist as unilateral deformity at any junction, bilateral deformities at the same junctions, or bilateral deformities at various junctions.

25.3 Types of Angulation Deformities of Lower Lateral Cartilages

Angulation deformities between footplate and the columellar segment cause divergent footplate deformity which has been renamed as type A A.D. These types of angulation deformities cause outward dislocation of the footplates. They are almost always reciprocally bilateral (Fig. 25.1) [4].

Angulation deformities at the columella-lobular junction between the columellar and lobular segment cause an increased angle of divergence, which results in a divergence of domes apart from each other that may cause broad and rectangular tip on the basal view which has been renamed as type B A.D [4]. These types of angulation deformities are also usually reciprocally bilateral. Widening of the divergence angle produces a long interdomal distance and a typical boxy nose (Fig. 25.1).

Angulation deformities between the lobular and the domal segment at the medial genu may form a very resistant acute angle at the medial genu of the dome which is usually unilateral and causes a medially distorted dome (Fig. 25.1). These types of angulation deformities have been named as type C A.D [4]. Any angle formation at the medial genu regardless of its degree is evaluated as a deformity because in normal anatomy medial genu curves circular at that region and we don't expect any angulation.

Angulation deformities between the domal segment and lateral crus at the domal junction may cause an abnormally concave lateral cruras and a pinched tip (Fig. 25.1). These types of angulation deformities have been renamed as type D A.D [4].

There are also abnormal angulations that are not located over junction lines of lower lateral cartilage. These have been called as angulation deformities not matching to junction lines. One of them is the angulation that distorts the columellar segment. These are usually bilateral, but not reciprocal. In this type of angulation deformities, the apex point of one abnormal angle is either pointed medially toward the opposite medial crus or laterally toward the nostril. If it is bilateral, the adjacent and compensating pair follows the same path parallel to the first one, and the apices of these bilateral angles point to the same side (Fig. 25.2). We have called this as type S A.D. due to its "S" shape. This deformity can be encountered anywhere over the columella [4].

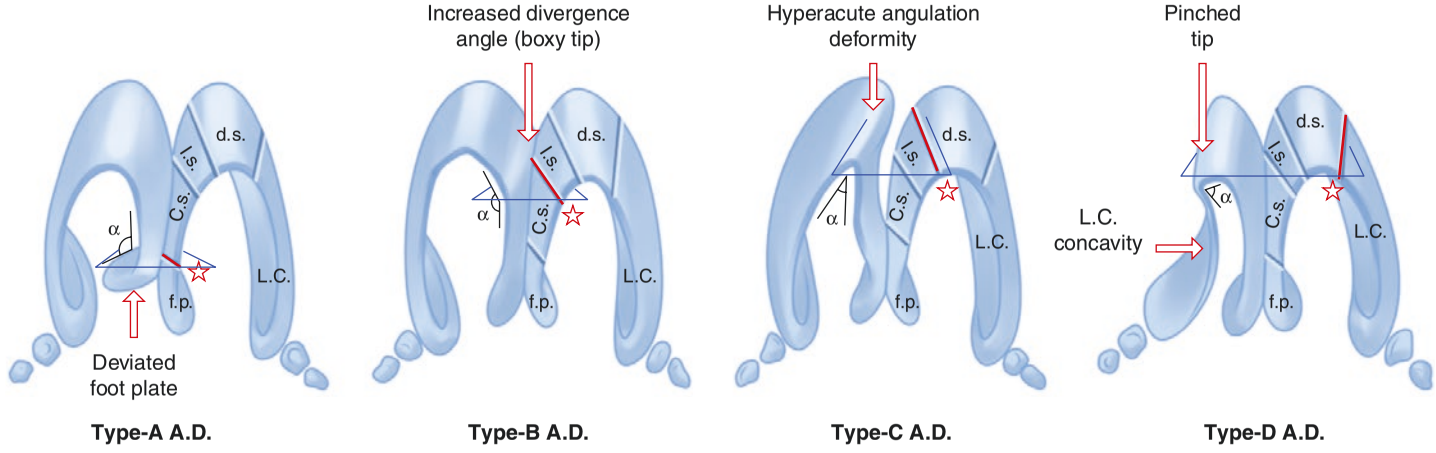


Fig. 25.1 Angulation deformities (A.D.) located over junction lines between segments and cruras of the lower lateral cartilages (LLC). Alpha angle shows the A.D. of each specific deformity. All A.D. at the right LLC is diagrammatically compared with the related junction line of the normal left LLC. Red lines together with red stars on the left LLC denote the specific junction line which matches to each type of deformity. *f.p.* footplate, *c.s.* columellar segment, *l.s.* lobular segment, *d.s.* domal segment, *L.C.* lateral crura

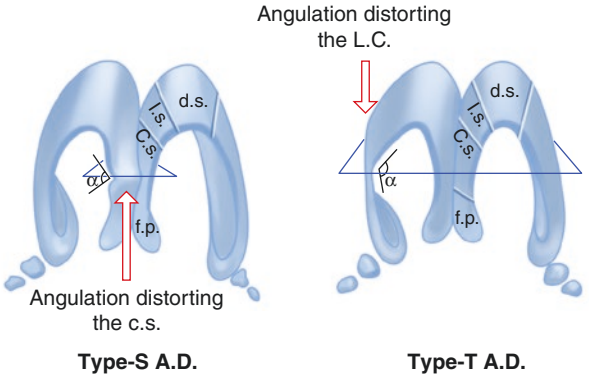


Fig. 25.2 Angulation deformities (A.D.) NOT located over junction lines between segments and cruras of the lower lateral cartilages (LLC). Alpha angle shows the A.D. of each specific deformity. *f.p.* footplate, *c.s.* columellar segment, *l.s.* lobular segment, *d.s.* domal segment, *L.C.* lateral crura

The other angulation deformity not matching to junction lines is the angulation distorting the lateral crus outward, usually located in the middle of the lateral crus. In this deformity, a dense, thickened area produces a lateral alar convexity 10 mm lateral to the dome on either one side or both sides. Bilateral lateral alar convexity produces a trapezoidal tip configuration in the anteroposterior and basilar views. This type of deformity has been mentioned by John Tebbetts previously [5]. Thus, we have renamed it as type T A.D. (Fig. 25.2). Any angle formation over the lateral crus regardless of its degree is evaluated as a deformity because in normal anatomy lateral crus is gently convex or straight throughout its length and we don't expect any degree of angulation.

25.4 Why Do We Need to Classify the Angulation Deformities?

A better understanding of an event or subject may be achieved by mastering the classification of the mentioned event or subject. Classification allows us to build algorithms, use a common language for the subject, and share and discuss data in a standardized and consistent manner over this common language. In his article, Hunter suggested, "choosing the most appropriate class is also important to the success of the classification system" [6]. For us, the most appropriate mainstay in the classification of nasal alar cartilage angulation deformities is the relation of these angles with anatomic junction lines; therefore we have classified the angulation deformities based on their presence over several junction lines. Such a classification of angulation deformities provides ease for recognition of these deformities and immediate preoperative planning for their restoration. In some cases, these problems may present in combination. In such circumstances, this classification provides an opportunity to deal with each individual deformity separately, enabling an analysis of complex contributions of a group of angulation deformities without any confusion.

Overall classification of angulation deformities based on the junction lines between the segments and cruras of lower lateral cartilages highlights the issue from

a different aspect, and anchoring each of previously described deformities plus the type C deformity over a common anatomical stratum, which formed a new concept never mentioned before, provides complementarity and integrity to the subject.

25.5 Causes of Angulation Deformities

The footprints and the causes for the formation of these angulation deformities should be traced back to the embryonic life. During the fifth week of embryonic development, medial growth of the maxillary processes results in the medial displacement of the nasal sacs [7]. During the course of this displacement, a slight reciprocal medial rotation of both nasal sacs is also observed. Some inadequacy in this rotational movement can possibly result in a larger angle of divergence which consequently causes a boxy nose, in other words, type B A.D.

The olfactory pit is surrounded by two ectodermally covered mesenchymal swellings, namely, the medial nasal process and the lateral nasal process. The merged medial nasal processes form the nasal tip, columella, philtrum, and complete upper lip. The lateral nasal processes begin to merge with the maxillary processes to form the lateral nose [7]. A certain variation in conjunctional adaptation between the medial and lateral nasal processes may result in angulation deformities at the level of domal junction, which may result in a concave lateral cruras and pinched tip, in other words, type D A.D.

Ventrolateral expansion of each medial nasal process causes compression of each nasal sac aperture into a slit-shaped opening [7]. This compression can sometimes result in an excess divergence of the footplates which may cause type A A.D.

Type S A.D. is most probably related to cartilaginous weakness at any level of the medial or middle cruras. For us, these hypotheses are the most plausible explanations for the formation of these deformities; however, they certainly need further clarification.

25.6 Restoration Techniques for Each Angulation Deformity

25.6.1 Type A A.D. (The Divergent Footplates)

While describing alar base surgery, Guyuron has not mentioned angularities in the footplate separately but named the region columellar base and described the footplates together with the muscle fibers and soft tissue in between as a whole. He divided columellar base deformities into four and classified the deformities in the caudal septum, maxillary spine, footplates, and soft tissue together [8]. The rationale for the treatment of the divergent footplates was arranged according to the degree of projection of the tip. If the patient exhibits an over-projected tip and divergent footplates, the lateral portion of the footplates will be resected partially and then approximated. If the tip is under-projected or has a normal projection, the divergent footplates will be approximated without resection [9].

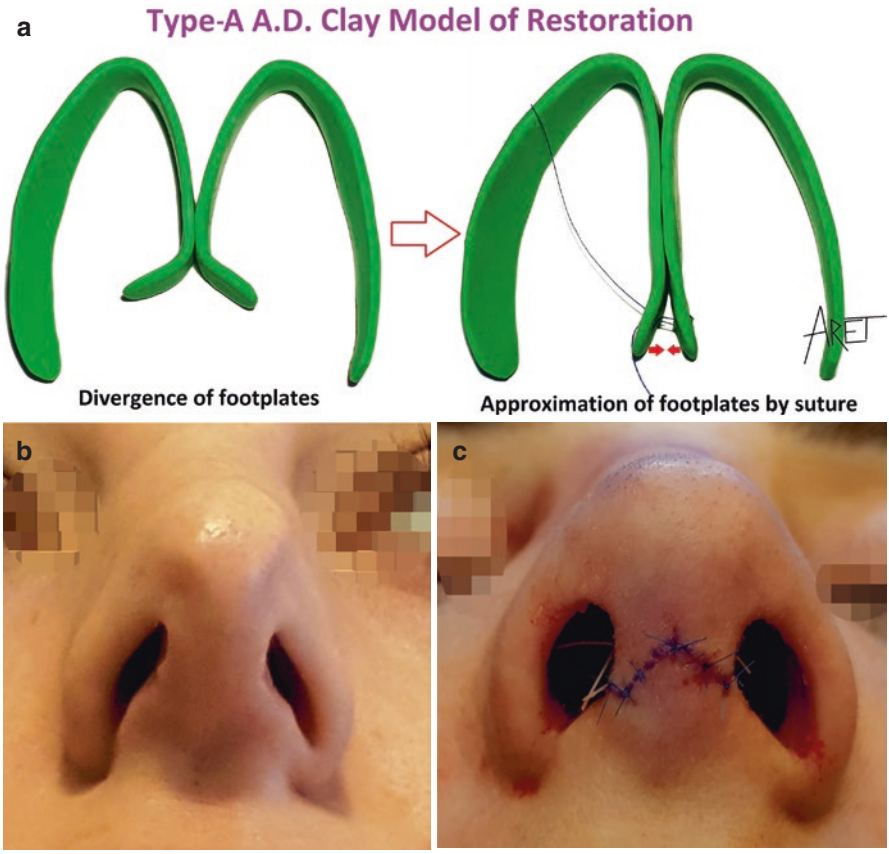


Fig. 25.3 (**a**) Clay model of restoration sequence of type A A.D. (**b**) Pre-op base view of a case with type A A.D. (**c**) Immediate post-op base view of a case with type A A.D.

Approximation of the footplates is done simply by approximating the footplates with U-shaped suture (Fig. 25.3) [4]. During the late postoperative period, some widening may occur with the use of absorbable sutures. Using a non-absorbable suture may also be considered to prevent the formation of this widening by making bilateral stab incisions over the mucosae of the footplates. In this case, hiding the knot very deep is crucial to prevent outward mucosal transpiercing of the knot which may cause undesired suture visibility through the nostril.

25.6.2 Type B A.D. (The Boxy Nose)

The term "boxy" is used throughout the literature in various ways. Sheen and Sheen described the boxy nasal tip as a square-shaped nasal base with a sharp angulation at lateral genu, related with a wide angularity between middle crus as much as 90° [10]. Rohrich and Adams divided this description into three classes

and included the width of the domal arc as a criterion in this classification. According to this classification, if the intercrural angle of divergence is greater than 30°, but the domal arc is normal (equal or less than 4 mm), this is called type I boxy nose. If the intercrural angle is normal (less than 30°), but the domal arc is widened (more than 4 mm), this is called type II boxy nose. If both intercrural angle divergence and domal arc are widened, then this is called type III boxy nose [11]. Constantian and Hanover acknowledge a malpositioning of the lateral crus in the majority of boxy tip cases and suggest that the boxy tip is rather rare in the presence of orthotopic lateral crus [12].

The operative goal is to reposition the tip-defining points, angulate the domes, and shape the lateral crura. In mild cases, conservative and non-destructive techniques are suggested. These conservative measures are cephalic trim (reduces the tip fullness and also decreases the distance between the tip-defining points), cartilage scoring (limited to anterior portion of the lateral crura), lateral steal [13], medial crural fixation suture (between cephalad borders of the middle cruras anterior to the point of divergence) [5], and different suture techniques employed in restoration and control of projection and rotation of boxy tips [14–17] which may help to correct the deformity.

But in severe cases, the correction of type B angulation deformities causing boxy tip was done by full-thickness cutting of the lower lateral cartilage from the vertex point of the angulation deformities (divergence angle) at the columella-lobular junction and then overlapping the lobular segment of the middle crus 3–4 mm down and medial to a columellar segment of the medial crus bilaterally after dissecting the underlying mucosae of lobular segments. Then the proximal lobular segment and the distal columellar segment was approximated with 6/0 PDS sutures. This maneuver brings the domes closer to each other and corrects the boxy appearance, and additionally, the overlapped lobular cartilage segments augment the columellar stability. Then again, a durable floating strut graft, proper lateral steal, and transdomal and interdomal sutures will complete the tip restoration (Fig. 25.4) [4]. The senior author always prefers to preserve the lobular segments and slide them down instead of sacrificing them which is always done in vertical dome division techniques [18–21].

The dome division technique was described by Goldman in 1957 and has been widely used and improved ever since. In this technique, he divided the alar cartilages lateral to domes and sutured them to the medial crura. This effectively produces a more triangular tip [13]. Although the tip might recover symmetrically, and results are generally reported as satisfying [20, 21], an optimal long-term recovery cannot be predicted in all cases because it is a destructive technique and visible problems such as crenation, alar retraction or bossa formation, alar rim collapse with pinching of the nasal tip, creation of a single tip-defining point, and rotation of the tip-defining points to more cephalad, thereby increasing infratip lobular height, might be encountered [13, 22]. Therefore, instead of using an aggressive technique for a boxy tip such as dome division, we propose to translocate the surgical intervention, out of the dome region toward the medial columella which is a more secure place. This intervention creates a new dome by bending

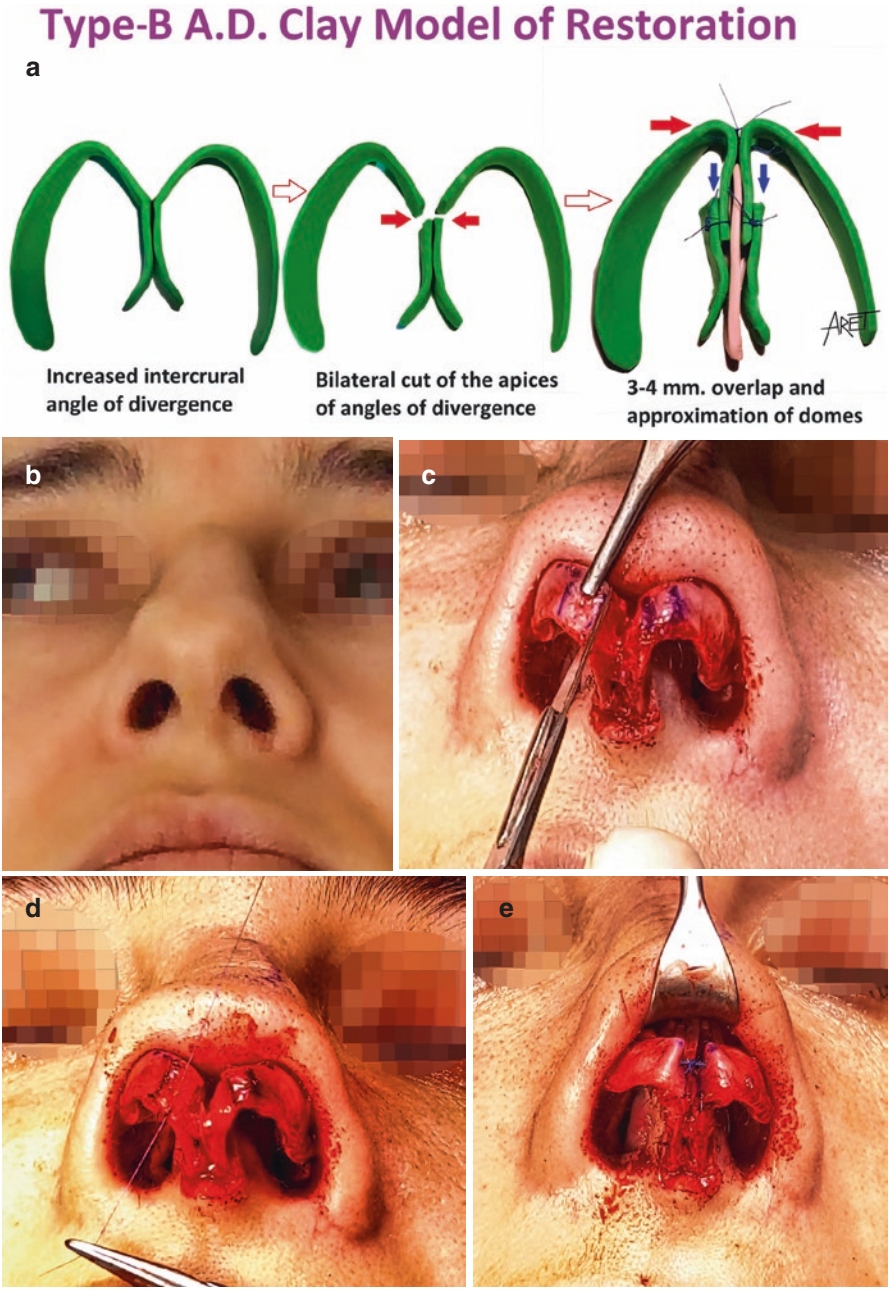
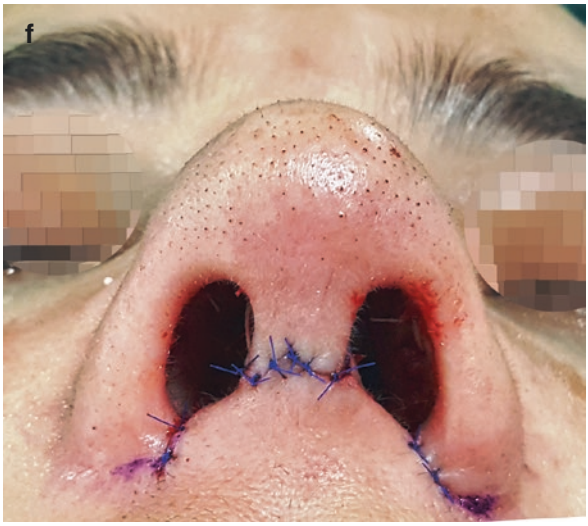


Fig. 25.4 (**a**) Clay model of restoration sequence of type B A.D. (**b**) Pre-op base view of a case with type B A.D. (**c**) The cut of the divergence angle. (**d**) The overlap of the lobular and columellar segment. (**e**) Transdomal and interdomal suture fixation after a lateral steal. (**f**) Post-op base view of a case with type B A.D.

Fig. 25.4 (continued)



the more lateral but undisturbed and integral alar cartilage segment with a lateral steal which makes the recovery period safer and more predictable. In cases with type B A.D., an overlap of 3–4 mm may cause unwanted bilateral mucosal outfolding toward the nostrils. These excess mucosae should be wedge-resected carefully and sutured primarily. As the mucosal resection is an irreversible execution, one should be cautious to do it at the very end of the restoration. These medial overlaps and resections will definitely reduce the anteroposterior diameters of nostrils to some degree which often provide a better look. Preserving a normal angle of divergence between the middle crura is usually desirable to preserve two distinct tip-defining points. Techniques that obliterate the divergence angle between the middle crura and excessively decrease the interdomal distance usually produce a single, non-anatomic tip-defining point [5].

25.6.3 Type C A.D. (The Acute Angulation at the Medial Genu)

The correction of type C A.D. was also done by full-thickness cutting of the lower lateral cartilage from the vertex point of the abnormal angle between the lobular and the domal segment and overlapping the proximal domal segment 1 mm down and medial to the lobular segment after dissecting the underlying mucosa. With this maneuver, the resistant angle can be eradicated. After a simple and proper lateral steal, the angulation was more medialized and hidden toward the columella and stabilized with the aid of a durable floating strut graft. The tip restoration is completed with the addition of transdomal and interdomal sutures and a cap graft (Fig. 25.5) [4].

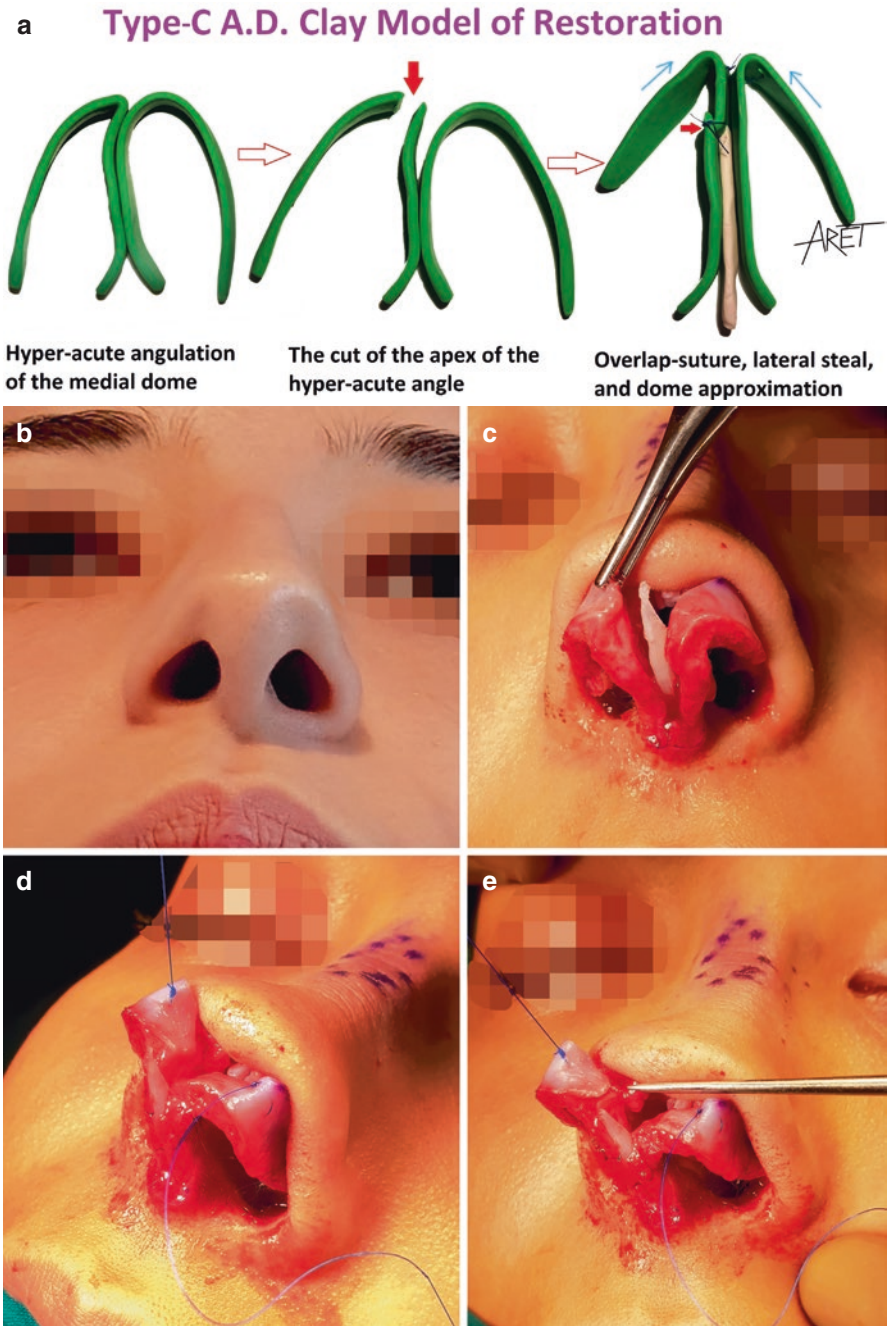


Fig. 25.5 (**a**) Clay model of restoration sequence of type C A.D. (**b**) Pre-op base view of a case with type C A.D. (**c**) Pre-op view of type C A.D. (**d**) Medialization of the angulation deformity with a lateral steal. (**e**) The cut of the angulation deformity. (**f**) The overlap of the domal and lobular segments. (**g**) Fixation of the transdomal and interdomal sutures and a cap graft. (**h**) Post-op base view of a case with type C A.D.

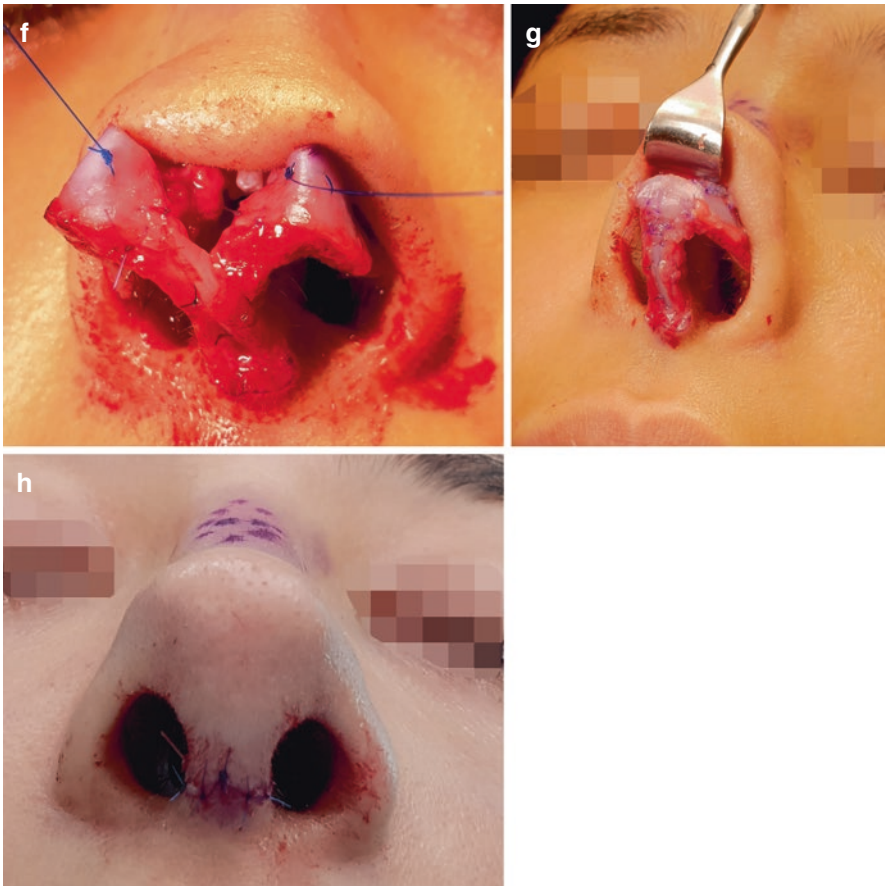


Fig. 25.5 (continued)

25.6.4 Type D A.D. (The Pinched Tip and Concave Alar Wings)

The correction of type D A.D. causing a pinched tip and concave alar wings can be performed by cutting the abnormal angle directly and then by applying reverse plasty to the lateral cruras [23–25]. Flipping, rather than excising, the excess cephalic lateral cruras [3] or augmenting the concave lateral crus by a camouflage graft bilaterally may also restore the deformity. The senior author has generally preferred the latter option in this series (Fig. 25.6) [4].

In most other angulation deformities, cephalic resection of the lower lateral cartilage was not performed, but the cephalic excess of the lateral crura was incised and placed under the lateral crura [26, 27]. However, in type D A.D. cases, the cephalic excess of the lateral crura was excised, because excision of the cephalic excess of concave lateral crura considerably reduces the concavity, and additionally the cephalic excess piece is used as an onlay graft over the lateral crura to camouflage the remaining concavity (Fig. 25.6).

The lateral crural strut graft might also be used in cases where lateral crural concavity cannot be resolved. Stable and invisible support is obtained when the crural strut graft is placed on the vestibular side [28].

25.6.5 Type S A.D. (The S-shaped Columellar Deformity)

The correction of type S A.D. was executed with regard to the degree of the resistance of the abnormal angle. If it was not very resistant, simply supporting it with a

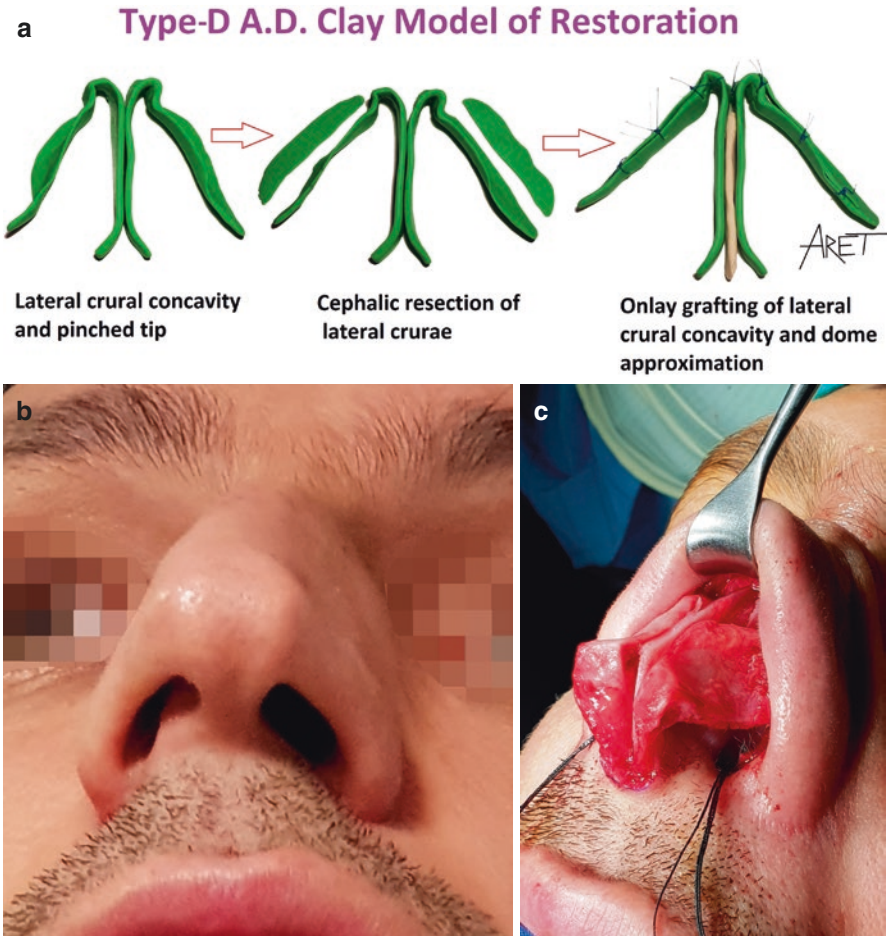


Fig. 25.6 (**a**) Clay model of restoration sequence of type-D A.D. (**b**) Pre-op base view of a case with type D A.D. (**c**) Pre-op view of type D A.D. (**d**) Design for shortening of the columellar segment (specific for this case due to long nasal tip). (**e**) The cut through divergence angle (specific for this case due to long nasal tip). (**f**) The overlap of lobular and columellar segment (specific for this case due to long nasal tip). (**g**) Camouflage of concavity with a mildly crushed cartilage graft and a cap graft. (**h**) Late post-op view of the case with type D A.D.

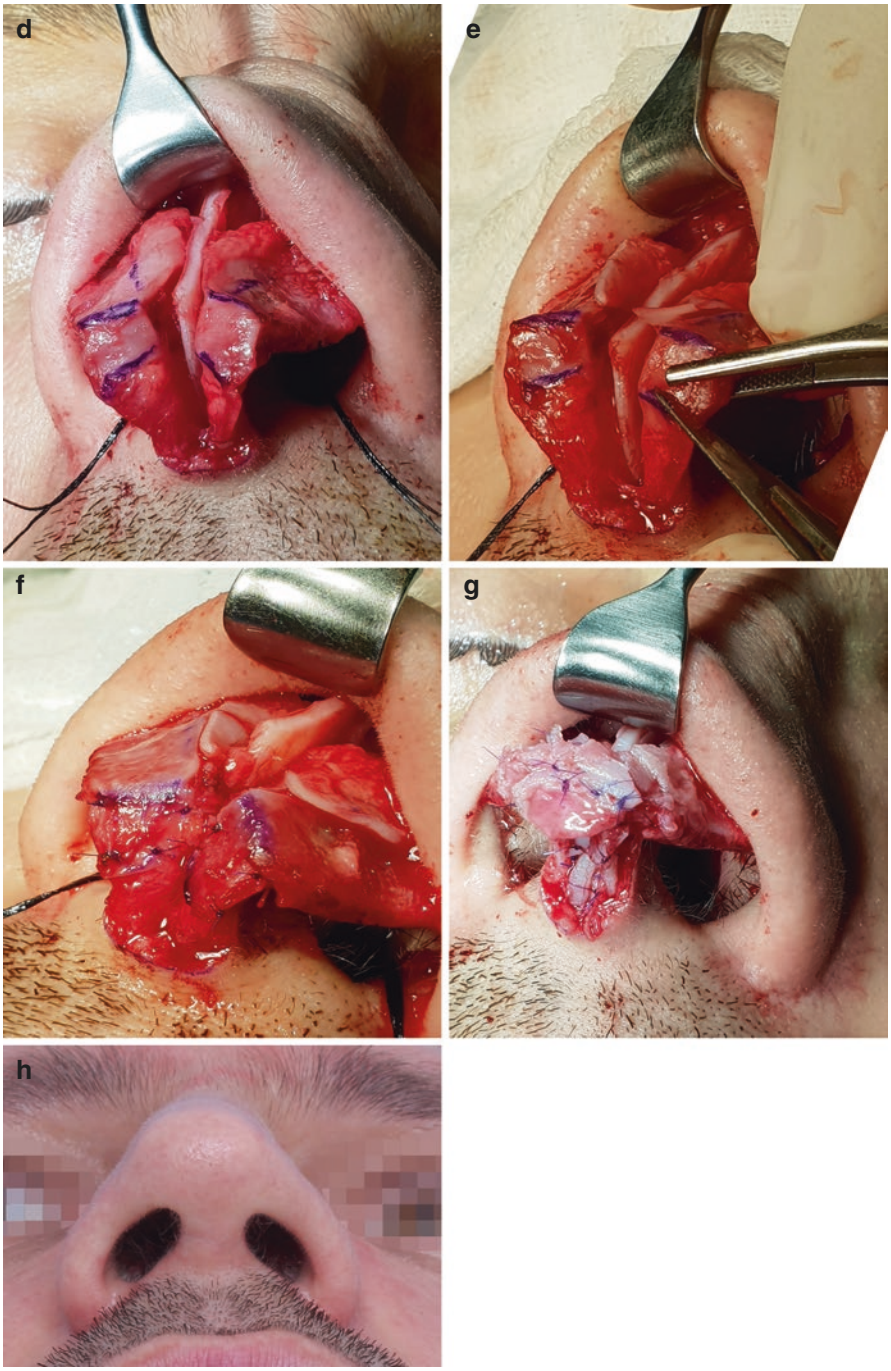


Fig. 25.6 (continued)

durable piece of a strut graft is enough to overcome the problem, because the strut graft support corrects the angulations at the columellar segment. However, if the abnormal angle is stiff or resistant to correction with a simple support of the strut graft, then it is recommended to break the resistance by cutting the vertex point of the abnormal angle and overlapping the proximal and distal parts of the columellar segment just 1–2 mm in length, dissecting the underlying mucosa of the proximal part of the columellar segment very little, and approximating the cut edges with 6/0 PDS suture. The resistance and the shape of the angles will disappear by overlapping the proximal and distal parts, so the shape can nicely be corrected (Fig. 25.7) [4]. This 1–2 mm overlap usually does not result in any loss in height of the columellar segment, since geometrically, the sum of the two sides of a triangle is larger than the opposite third side. So, if the normal height of the columella and the abnormal angle rays are thought as a triangle, the sum of the length of two rays forming the abnormal angle will be larger than the normal columellar height. Still, even if any shortening of the columellar length occurs, it can be compensated by little more lateral steal. Then a durable piece of a floating strut graft and transdomal and interdomal sutures will suit well to nicely reshape the tip. If these types of angulation deformities are left untreated, it might distort the columella or may displace the strut graft toward the opposite side, resulting in asymmetry or deviation either immediately or in the late postoperative period.

25.6.6 Type T A.D. (The Lateral Alar Convexity)

Restoration of type T A.D. has been mentioned by Tebbetts. He suggests that if it is present bilaterally and located more than 5–6 mm lateral to the dome point, lateral alar convexities are best corrected with crural spanning sutures. Occasionally, lateral alar convexities occur within 5 mm lateral to the dome. In this position, dome-spanning sutures can usually correct the deformity. The rare unilateral lateral alar convexities require a unilateral crural spanning suture from the lateral alar convexity to the dorsal septum [5]. The lateral crural spanning suture may cause external valve dysfunction and alar retraction [29]. That's why the senior author has preferred to cut the angle causing deformity tangentially than to approximate the cut edges of lateral crura end to end without overlap (Fig. 25.8) [4].

In all of the abovementioned restorations, a cap or shield graft may be utilized. The main purpose for the utilization of these grafts is increasing the tip projection. Cap graft has been used in all of the cases in our series with angulation deformities. Type B, C, and S angulation deformities may need extra tip augmentation due to possible loss of the projection caused by cartilage overlaps during their restoration. The management of type A, D, and T angulation deformities do not require cartilage overlap; thus, the loss of projection is not expected. However, I prefer to

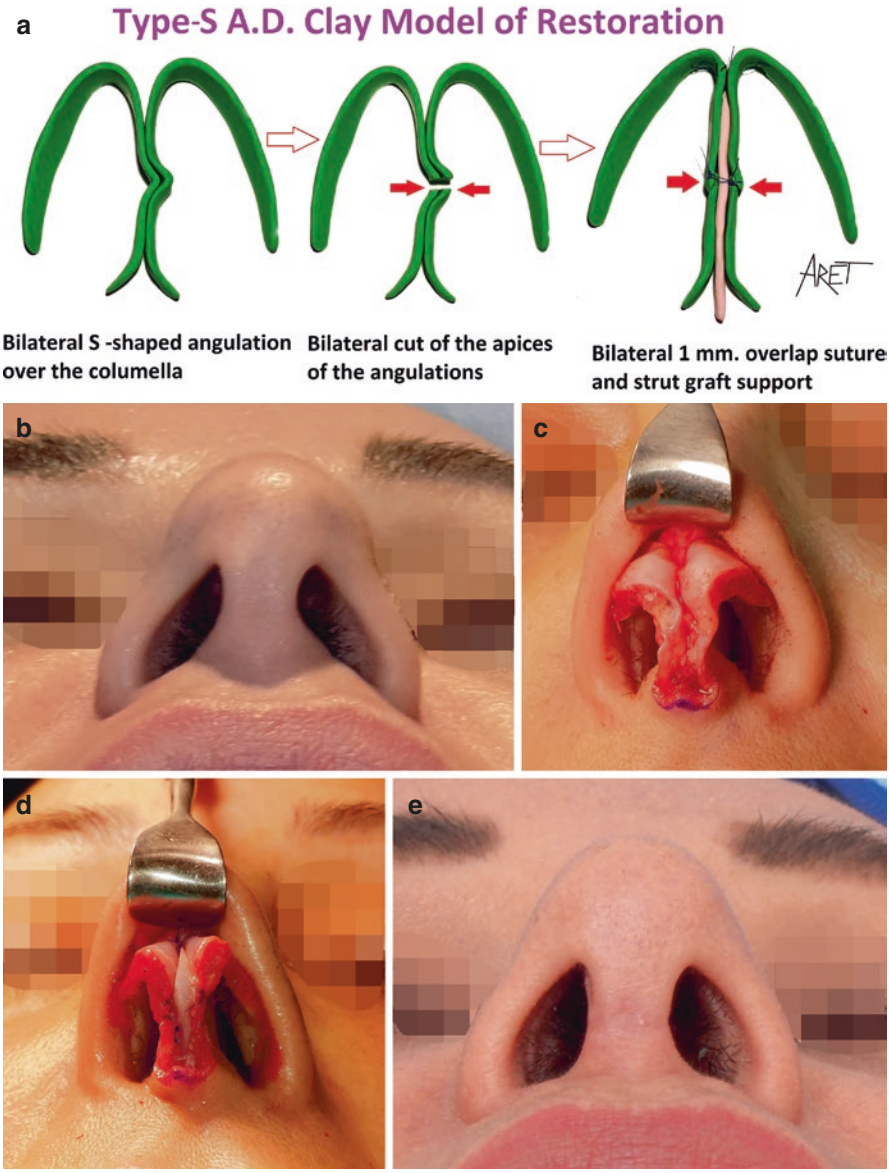


Fig. 25.7 (**a**) Clay model of restoration sequence of type S A.D. (**b**) Pre-op base view of a case with type S A.D. (**c**) Pre-op view of type S A.D. (**d**) Deformity corrected with cut of angulations and overlap, strut graft, and transdomal and interdomal sutures. (**e**) Post-op base view of the case with type S A.D.

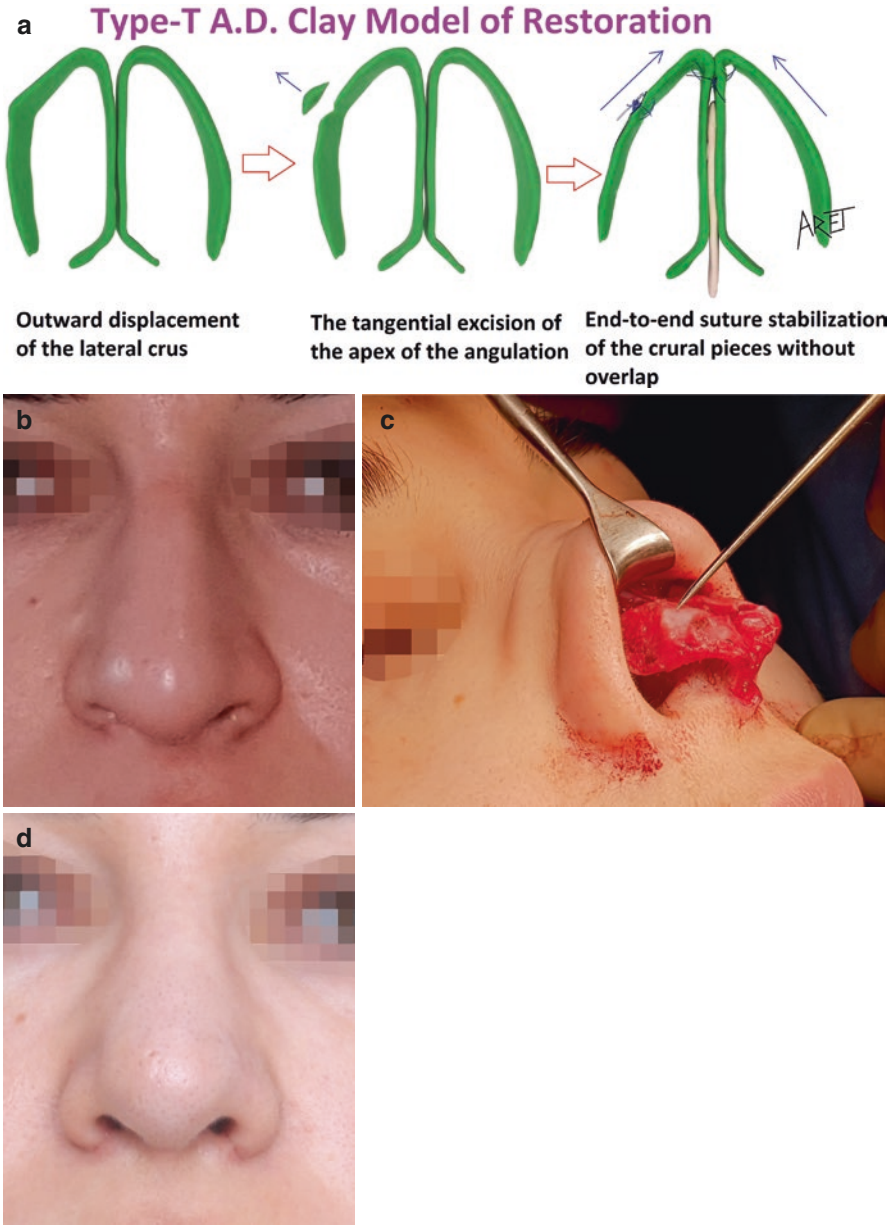


Fig. 25.8 (**a**) Clay model of restoration sequence of type T A.D. (**b**) Pre-op anterior view of a case with type T A.D. (**c**) Pre-op view of type T A.D. (**d**) Post-op anterior view of a case with type T A.D.

use the cap graft which usually gives a better definition of the nasal tip if placed properly. The cap graft can be camouflaged by crushed cartilage or soft tissues. The use of the fascia is another wise alternative to camouflage minute irregularities at the tip region. I prefer to talk about the possibility of the use of a fascia in primary rhinoplasty patients only when I examine that the nasal skin is very thin or sun-damaged. In case of any graft visibility despite all precautions, fillers may be utilized to solve the problem. I don't use any filler in patients not having the previous rhinoplasty, but I cautiously and selectively use hyaluronic acid in correction of minute deformities of previous primary or secondary rhinoplasties of only my own patients because the fillers are not very innocent but may cause complications such as hypersensitivity, infection, and most importantly catastrophic vascular occlusions. I usually pierce the needle perpendicular to the sub-SMAS region at the midpoint of the cap graft border and then pull the plunger back and wait 4–5 s to control possible vascular puncture; if there is no blood, then I gently push the filler in the form of small droplets around the graft border till the graft visibility subsides.

The necessity of the strut graft has recently become a matter of debate since there is evidence in the literature about the redundancy of the utilization of a strut graft [30]. However, a properly designed columellar strut graft can result in greater tip projection and lengthening of the columella [31]. I prefer to utilize the strut graft in all rhinoplasty cases. Additionally, utilization of a strut graft in cases with especially type B, C, and S angulation deformities is an obligation, because the strut graft is the main supporter of the medial cruras in these cases after several cuts and overlaps at angulation apices. It is never recommended to resect a segment of medial or middle crus without reconstructing the crus over a strut to prevent bending or kinking at the point of resection under postoperative wound contraction forces [5].

Especially type C and type S A.D. may present as hidden deformities since they sometimes do not distort the tip shape and are difficult to determine preoperatively. It is suggested that if a deformity does not show externally, its correction may not be necessary. Besides, a correction may even be detrimental, since it can introduce unexpected additional variables and decrease the predictability of achieving overall balance in external appearance [5]. Nevertheless, especially in open approach rhinoplasty, after performing dissections during the operation, all the preexisting balances change due to detachment of several of the abovementioned essential ligaments, attachments, and other soft tissues that support the lower lateral cartilages. Thereafter, the assumption that previously innocent preoperative deformities would not cause any trouble postoperatively may result in disappointment. Thus, all of the angulation deformities should be restored without any exceptions. The mild forms may initially be restored by using sutures or by the help of grafts; however, the results may be unpredictable when left untreated.

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Preservation Rhinoplasty

26

Seçkin Ulusoy, Cemal Cingi, and Yves Saban

26.1 Introduction

The development of rhinoplasty has occurred through a number of stages, such that it has now become a genuine cosmetic procedure which depends on careful analysis prior to surgery, planning of the operation to be carried out and the actual procedure itself. Joseph was the first to popularise rhinoplasty, with a procedure aimed solely at reducing the nasal features. This then developed into a mixture of both reduction and graft placement at the first rhinoplasty. Revision or secondary rhinoplasties at one time were associated with very poor outcomes by current standards. In the third stage of rhinoplasty development, these outcomes underwent a vast improvement. Following these improvements, the humble "nose job" turned from a task a jobbing surgeon rushed to complete a procedure aiming to produce a natural-appearing, beautiful nose that can work healthily [1].

Closed rhinoplasty was very much the dominant approach to rhinoplasty at one time, but the open approach developed rapidly into a competing procedure. Pioneers in the open approach were Goodman [2], Anderson [3], Daniel [4, 5] and Gunter [6], amongst others. These surgeons were soon followed by others. But why did surgical practice suddenly undergo a switch in approach? The answer lies in three aspects of the open approach. In the first place, an open procedure provided a better opportunity to see what was happening, which made analysis and teaching more straightforward, as well as the procedure itself. Secondly, technical advances, such as nasal tip suture or advanced repair of the septum and the midvault, were only

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_26

feasible in the open approach. Finally, surgeons could acquire expertise in open rhinoplasty more readily than closed procedures, and the range of suitable surgical candidates widened to take in individuals from all over the world. Following these surgical advances, rhinoplasty has become a highly popular and commonly undertaken cosmetic surgical operation.

26.2 Preservation Rhinoplasty

Reduction rhinoplasty was first undertaken in 1898. Joseph took a genuine open approach and split hump technique to reduce a deformity, whilst Goodale, working in Boston, carried out an endonasal subdorsal septal excision whilst depressing the dorsum. Cottle afterwards pioneered a different procedure – septal release to depress the dorsum. However, the rhinoplasty procedure of Joseph remained the most popular, even though excising the hump was a destructive act and an open roof could only be provided by medialising osteotomies. Since the procedure always resulted in the collapse of the middle third of the dorsum, a range of methods were developed to minimise this unwanted outcome, namely, spreader grafts, flap and camouflage grafts [7].

It is natural that as nasal anatomy has been better appreciated in more recent times, in particular how the dorsum is configured, the discovery of the superficial musculoaponeurotic system (SMAS) and certain nasal ligaments, this more sophisticated picture has led surgeons to favour less radical operations of a less destructive kind, whereby there is no call for the complicated revision surgery needed when the skeletal framework of the nose is destabilised, especially in the area of the mid nasal vault. Preservation rhinoplasty works on the principle that the skin compartment, SMAS and sophisticated ligamentous network should be untouched and the dorsum preserved as it was before surgery. However, the dorsum should function as a hinge, by separating it from the root of the pyriform aperture and by freeing it from the septum [7].

Preservation rhinoplasty has developed from anatomical research, the advances in suturing methods for the nasal tip and advances in operative practice. The last 10 years have witnessed a great leap in anatomical understanding of the nose and how the basic structure determines the beauty of a nose and the way it should be treated at operation. Two aspects in particular are now better appreciated—the way the soft tissues are composed, not forgetting the ligaments of the nose, and the bone and cartilage constituting the vault. For many years, little attention was given to the nasal ligaments, despite their central role in preserving nasal function and providing the nasal contours [8]. The vertical scroll ligament lends stability to the internal nasal valve by its attachment to the transversalis muscle. Rejoining the ligament can sharpen the alar groove and improve valvular function [9]. The bony hump has been demonstrated in studies utilising anatomical dissections to act as merely a bone cover over the cartilages that form the vault. Removing it with a rasp is straightforward. The keystone is also better understood nowadays as a joint between bone and cartilage with some limited movement. Its outward bulge can be flattened out through resection of the cartilage of the septum [10].

Cakir [11] observed that even finer control and lower complications could be obtained with a closed procedure involving tip suturing than with an open operation. The aim of the closed procedure was the preservation of the ligaments in the nose and manipulation of the cartilaginous structures without the extensive need to resect. Furthermore, Cakir noted a subperichondrial procedure causes fewer issues post-surgically (such as oedema or the absence of sensation), and when revision surgery was called for, the lower amount of scarring with this approach, as opposed to traditional open procedures, meant more straightforward surgery was usual [12]. Other ways in which the practice of tip surgery has developed considerably are cephalic alar preservation and alar tensioning. It was formerly routine to excise the superior lateral crus when carrying out rhinoplasty, but it has been shown by Ozmen et al. [13] and Gruber et al. [14] that if the whole of the lateral crus is kept intact, this will have the benefits of reducing alar notch formation and making alar rim grafting less necessary. Surgery for a malpositioned ala has long been viewed as amongst the most challenging of tip defects to rectify. The traditional approach was to transpose the ala and graft struts in the lateral crural region. Both Cakir [11] and Davis [15] have challenged conventional wisdom by demonstrating clearly that the ala does not need to be transposed and that the application of tension in the medial direction is sufficient, with no need to resect the ala or graft extraneous material.

The conventional rhinoplasty calls for the dorsum to be resected as a key element. Resection obliterates the keystone region and necessitates both osteotomies and reconstruction of the middle nasal vault. Most reconstructive surgery that uses graft material from the patient's rib is to rebuild the dorsum in a secondary operation. Just as Goodman helped to make the open approach of Rethi more acceptable to surgeons [2], Saban's modernisation of the push-down operation helps to keep the dorsum intact [16]. Saban's approach, whereby the dorsum is conserved, gets around the necessity for immediate reconstruction of the middle nasal vault in primary surgery and allows revision to proceed step by step, in contrast to the radical nature of procedures using grafts obtained from the rib.

26.3 The Difference between Preservation Rhinoplasty and Structural Rhinoplasty

The majority of rhinoplasties involve dissection in the layer beneath the SMAS. By doing this, the surgeon ends up dividing the vertical scroll ligament and the Pitanguy ligament, which is a deeper portion of the SMAS functioning to hold up the domes in the region of the nose tip. Division of these ligaments reduces the support for the roof, can produce dysfunction of the nasal valve and may give rise to the soft tissue anomaly known as pollybeak. Excision of the SMAS is sometimes undertaken during structural rhinoplasty with the incorrect justification of reducing the thickness of the skin or its bulk. A structural rhinoplasty then relies on a grafting technique to reconstruct the nose. However, this technique typically needs large amounts of grafts [7].

By contrast, subperichondrial and subperiosteal dissecting techniques do not damage the nasal ligaments. The cartilaginous structures of the tip are altered in a

different manner, by mobilising them and performing a limited resection of the septum below the dorsum and then lowering the dorsum in its entirety by hinge action. The dorsum is not touched by this technique, and thus, there is no call to reconstruct the vault and no need for grafting [7].

Preservation rhinoplasty refers therefore to an operative approach that preserves the skin compartment, SMAS and the nasal ligaments [7].

The keystone area is at a different level medially and laterally. The dorsum can hinge after being freed laterally and from the underlying septal region. If the osteocartilaginous junction is divided, particularly where the bones are not too long, hingeing may also be possible [7].

Preservation rhinoplasty can be carried out via either an open or closed approach. A key element is entering the subperiosteal plane for dissection, which is technically challenging and requires practice. The SMAS is conserved, together with the ligaments, and there are no dead space results. Oedema is less and post-operative recovery swifter [7].

In candidates for preservation rhinoplasty, the dorsum may already be aesthetically appealing, although possibly too raised or deviating laterally. Osteotomies may be placed low and laterally, transversely and across the nasal root. Unlike in Joseph's rhinoplasty, the osteotomies are performed at points where the overlying soft tissues are abundant. This choice of site reduces the chance that any subsequent roughness will be visible externally [7].

26.4 Indications and Contraindications for Preservation Rhinoplasty

26.4.1 Indications for Primary Cases [7]

- Candidates have a normal-appearing dorsum that projects
- too far forwards (i.e. tension nose) with a septum that does not deviate laterally.
- Nasal bones are short, the cartilage causes the nasal hump, and the root of the nose is normally situated.
- The dorsum is straight in appearance but does not lie in the midline, particularly in men.
- The candidate is older and has a nasal hump with a thin skin compartment.

26.4.2 Relative Indications [7]

Primary cases:

- The lower septum deviates from the midline.
- There is the deformation of the septum, the septum may lose its stability, or there are angulations or spurs.
- The root of the nose is more posterior than usual, and the dorsum assumes an s-shape in profile view.

- The dorsum is broadened.
- The mid-third of the nose has a slight degree of asymmetry.

26.4.3 Contraindications [7]

- Revision surgery following earlier primary rhinoplasty by another surgeon.
- Prior submucosal septal resection.
- Highly asymmetric mid-third due to deviated septum, dorsal aesthetic lines bowing outwards or inwards, upside-down "v" deformity.
- Saddle nose where augmentation is necessary.

26.5 Preservation Rhinoplasty Technique

At present, preservation rhinoplasty is revolutionising surgical aesthetic practice, as it results in a more natural appearance and mandates a shorter recovery period. The technique is not associated with several problems which occur post-surgically in traditional rhinoplasty. The decision about conserving the dorsum of the nose depends on analysing the dorsum and evaluating any deformity, in particular how any deformity is marked and of what exact kind [17].

The indications for the preservation of the dorsum are highly specific. The operation is a primary procedure suitable in individuals whose dorsum has a good appearance and the only need is for the dorsal line to be lowered. In such individuals, an open approach to preservation rhinoplasty is possible. The skin should not be raised in the dorsal region, and thus, the ligaments will be conserved in almost their entirety [17].

26.5.1 Surgical Procedure

Goksel and Saban [17] describe using an inverted v-shaped incision with an open approach to deal with deformity consisting of a minor hump in the dorsal region, both of the bone and the cartilage. Rasping is not used when the ligaments are conserved and the SMAS is not touched in the area of the dorsum. Whilst the skin and SMAS are dissected, a tunnel is produced to provide access for the osteotomies to be performed laterally and transversely. Approach to the piriform aperture is from the side in the vicinity of the vertical scroll ligament. The scroll ligament and Pitanguy's ligament are conserved, and the skin of the nose is not lifted up [17].

A piezoelectric device can be used to perform the osteotomy, the instrument being introduced through the tunnel described above. The septum is incised in a hemitransfixation manner after dissecting in the subperichondrial plane. The scalpel and dissection scissors are used to remove a strip of septal cartilage, according to how much lowering is sought. The incision reaches to the perpendicular ethmoid, and the osteocartilaginous junction is divided. The caudal portion of the

cartilaginous septum is conserved. A 2 mm baby rongeur (Ada Medical Instruments) is utilised to excise the superior portion of the perpendicular plate of the ethmoid and reduce its size [17].

A triangle of bony is removed (Webster triangle) in the region of the piriform aperture. This stops the inferior turbinate from obstructing the nose when the dorsum is lowered. The piezoelectric device is employed for osteotomy in the sagittal direction at the level of the facial groove. This osteotomy renders lowering the dorsum more straightforward. The cut edge is parallel to the sagittal plane, and the dorsum has greater room to be pushed down, avoiding problems such as remaining nasal hump or a new hump developing later. Transverse osteotomy is carried out bilaterally, and these osteotomies are joined with a further incision made with a 2 mm osteotome [17].

These osteotomies need to be done exactly, after which the periosteum is dissected off the maxillary inner face to prevent friction when the dorsum is depressed and to provide the necessary space. Dissect the area bounded by the upper lateral cartilages and the nasal bones. The keystone area needs to be freed in three dimensions, so that it can be moved downwards and the dorsum reshaped. The lateral connections are loosened, and thus, the desired movement of the dorsum is possible. A hump should not be able to re-form. If this part of the procedure is not done correctly, the dorsum can be depressed but not reshaped, and therefore, it will not be possible to achieve a straight dorsum [17].

To ensure the hump is reduced in as safe a manner as possible, the following steps need to be taken in order [17] (Figs. 26.1 and 26.2):

1. The septal cartilage must be resected, and the osseous and cartilaginous portions of the septum must be free from the dorsum, or else, unplanned fractures may occur during dorsal lowering.
2. The Webster triangle must be removed from the piriform aperture to stop the inferior turbinate blocking the nose.
3. The periosteum must be lifted off the inner maxillary surface to prevent friction occurring.
4. Dissect laterally to separate the upper lateral cartilage from the nasal bones to allow for the dorsum to be set straight when being depressed.
5. Score the remaining cartilage underlying the keystone region of the dorsum.

Once all the parts of the procedure related to the dorsum have been carried out, the tip needs to be reshaped. An inverted v-shaped transcolumellar incision is performed, and the lower lateral cartilages are dissected in the supraperichondrial plane. The lateral crura are freed from the skin of the vestibule. Lateral crural strut grafting allows the crura to be reshaped in a flatter form. Then, those grafts were placed into the pocket created in the direction towards the lateral canthus and fixed them with 5.0 Vicryl (Ethicon, Inc.). The medial crura receive extra support, and their height is made symmetrical with columellar strut grafting. Sutures which pass through the skin hold the lateral crura in place and assist with creating the desired crural outline [17] (Figs. 26.3, 26.4, 26.5, and 26.6).

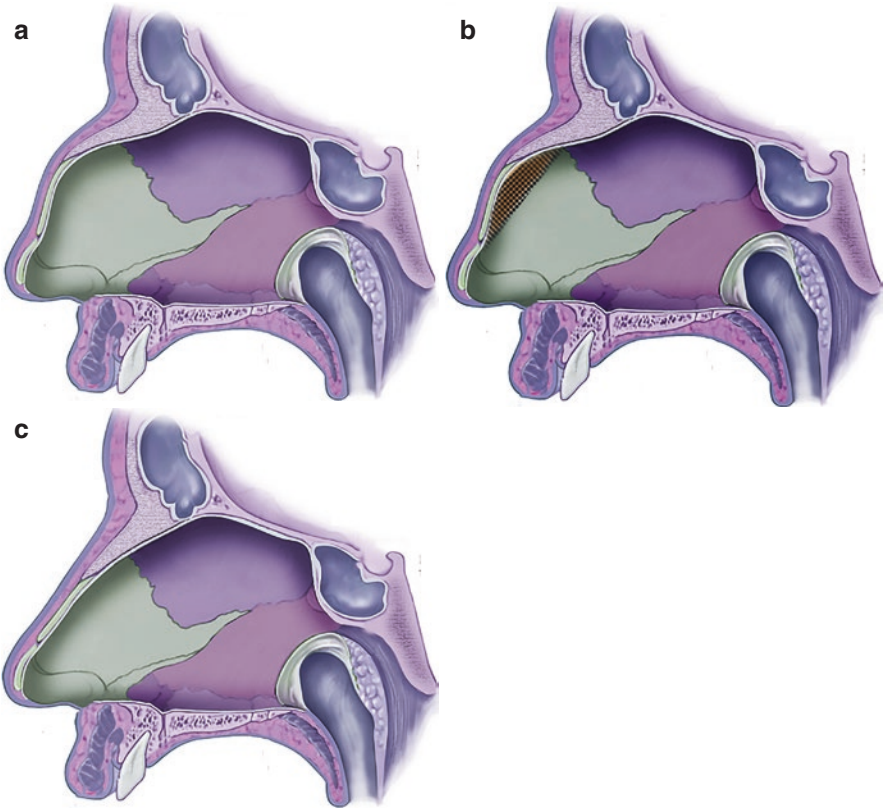

Fig. 26.1 (**a**) Preoperative view of the lateral wall. (**b**) Resection area planning. (**c**) Post-operative view of the lateral wall

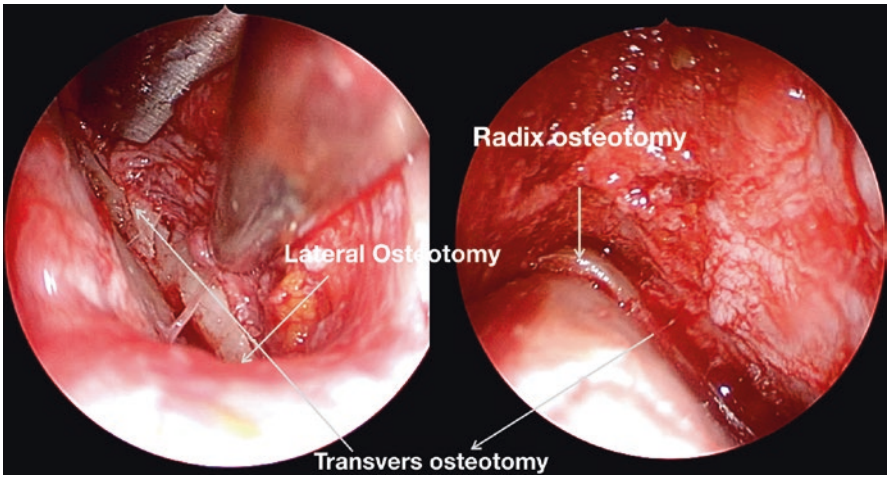

Fig. 26.2 Intraoperative view lateral, transverse and radix of osteotomies

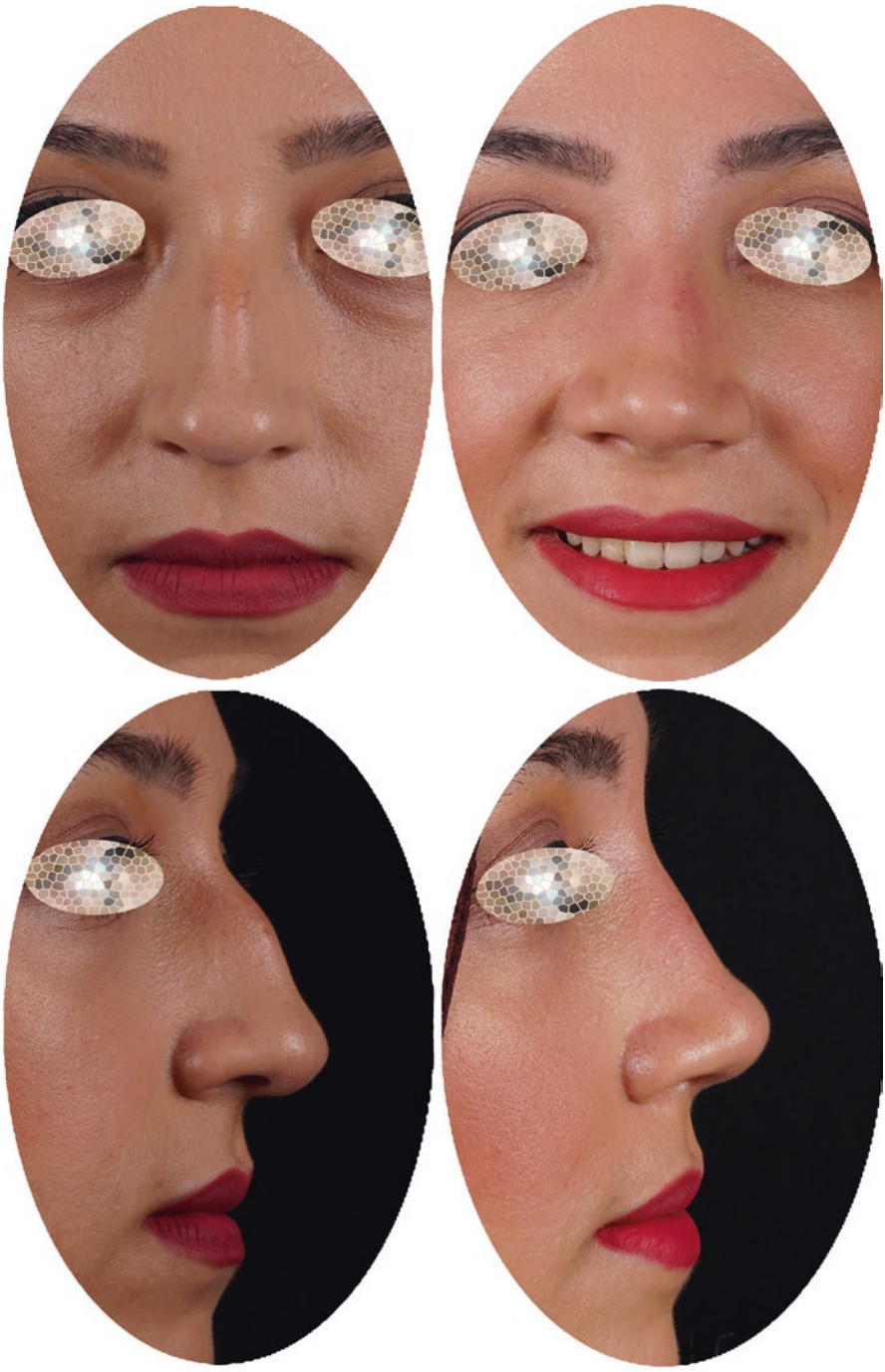

Fig. 26.3 Preoperative and post-operative views of a patient

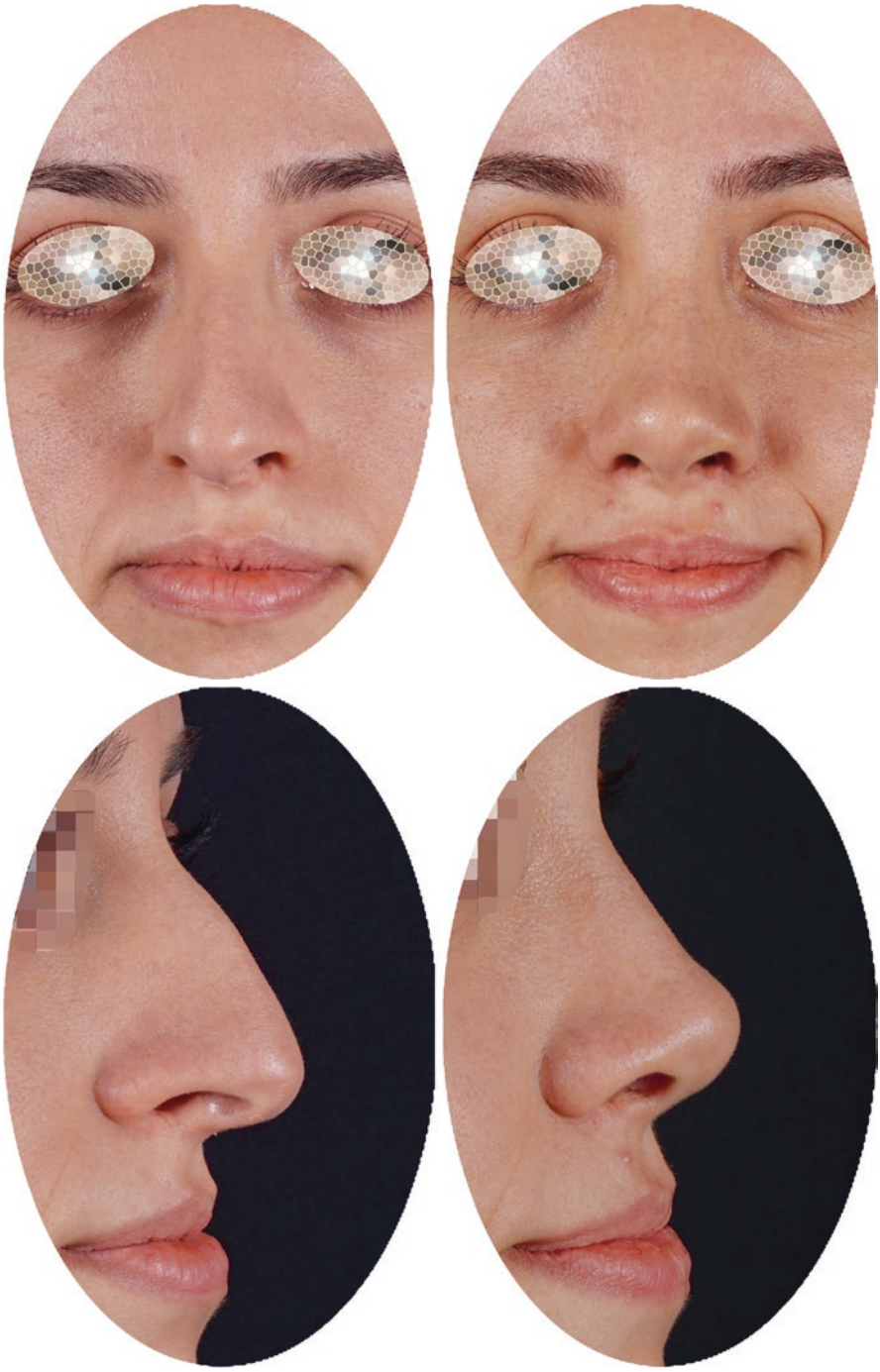

Fig. 26.4 Preoperative and post-operative views of a patient

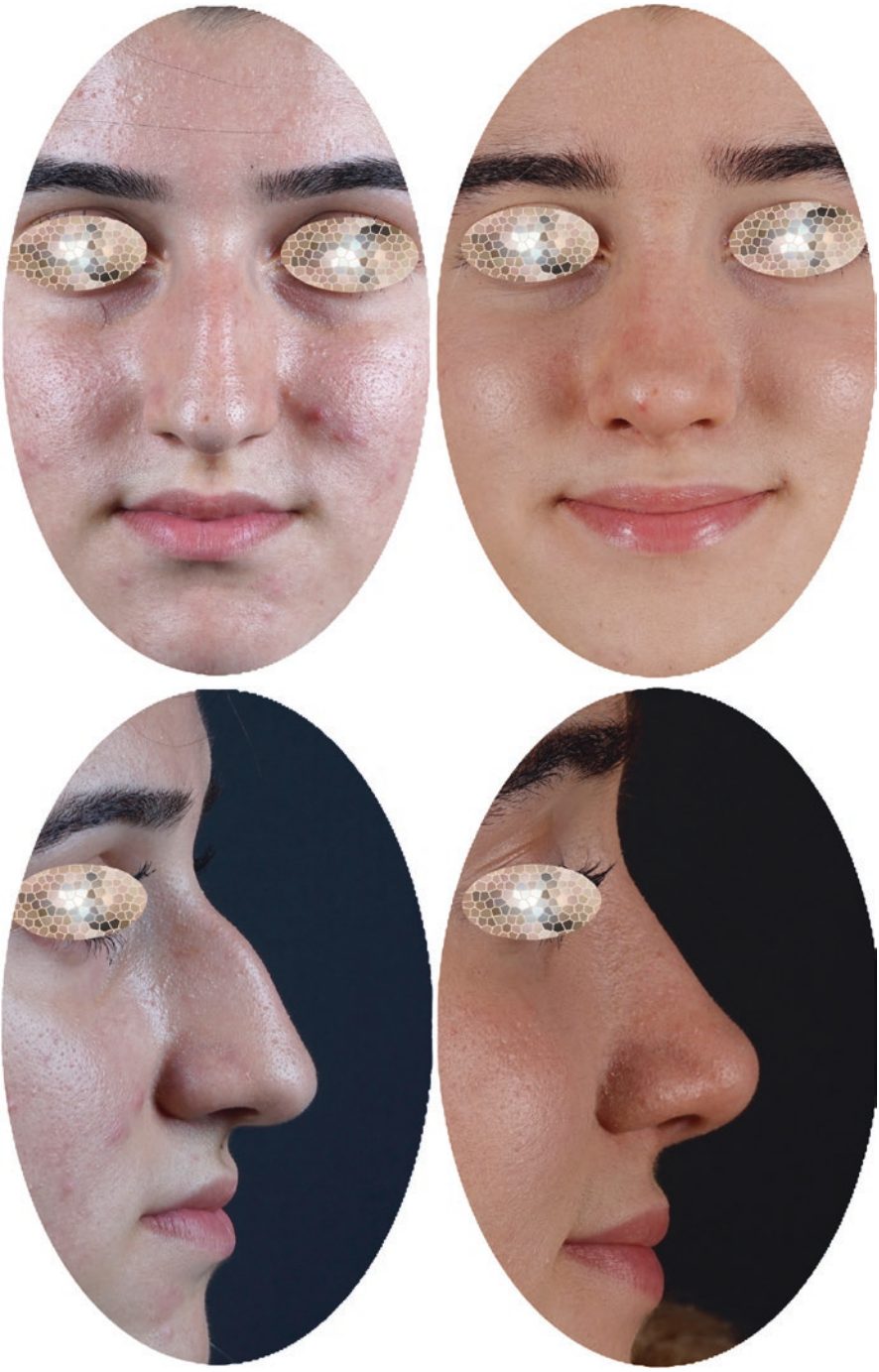

Fig. 26.5 Preoperative and post-operative views of a patient

Fig. 26.5 (continued)

26.6 Can Preservation Rhinoplasty Result in Nasal Airway Obstruction?

Flow of air through the nose is guided towards the middle turbinate by the nasal valve. Because the middle vault is undisturbed, this process is unaffected. Preserving the dorsum of the nose means that transnasal flow of air improves marginally as the angle between the upper lateral cartilages and the vault of the septum opens slightly. This happens regardless of whether the procedure is "let-down" (involving resection of the Webster triangle) or "push-down" whereby the maxilla ends up facing the inner side of the piriform aperture [7].

The removal of a portion of the septum from beneath the dorsum coupled with the mobilisation of the entire dorsum allows the surgeon to move the nasal bridge into a new position. The key decision is about whether to hinge about the root of the nose or to drop the dorsum. The choice is determined by where the nasal root is located and whether it should remain in that position or not. This in turn dictates whether resection and incision of the perpendicular plate will be required [7].

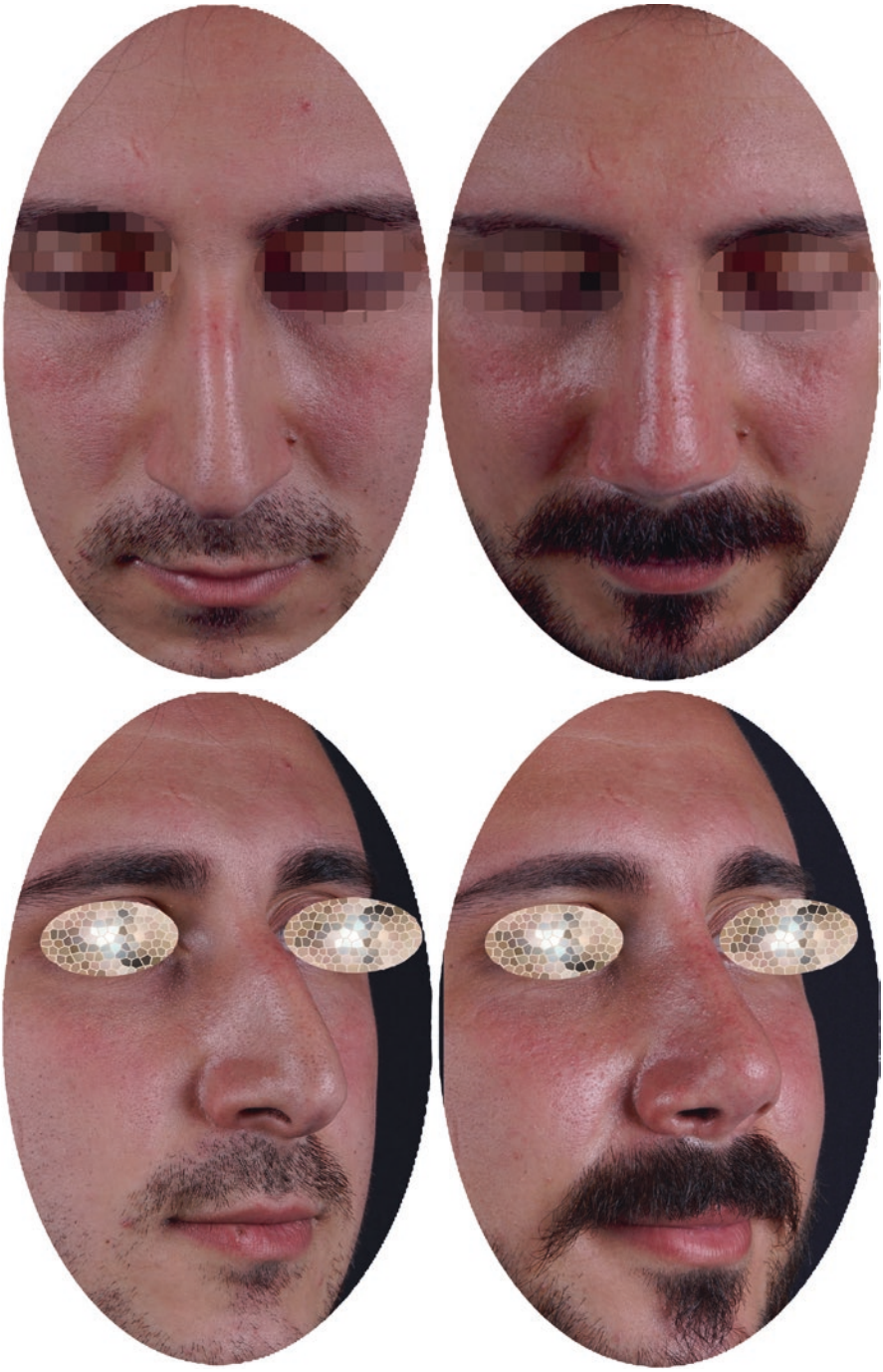

Fig. 26.6 Preoperative and post-operative views of a patient

26.7 What Are the Issues Associated with Preservation Rhinoplasty?

The principal problems are a remaining hump (due to the lack of flexion in the keystone area), the tendency of the dorsum to deviate to one side and an excessive degree of supratip depression if the cartilage has been excessively excised at the anterior septal angle. These issues are generally straightforward to prevent or to remedy later. If the degree of surgery required on the septum is very large, the lower two-thirds of the nose may be inadequately supported, and a structural rhinoplasty may be needed [7].

An appreciation of the philosophy behind preservation rhinoplasty lets surgeons use elements from the procedure routinely, so as to lessen the need to take cartilage from the septum and to conserve the SMAS and the nasal ligaments. An adoption of the preservation mindset may result in fewer complicated rhinoplasty revision operations [7].

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Suture Lift of the Nasal Tip

27

Sinan Eroğlu, Cemal Cingi, and Grant S. Hamilton III

27.1 Introduction

Suspension suturing is a frequently employed technique in various kinds of facial plastic surgery, including rhinoplasty, where its use has been reported by multiple authors [1–3]. Many patients who want rhinoplasty have a dorsal hump with under-rotation and under-projection of the tip. In such cases, a full rhinoplasty may well not be needed [1]. Tailoring the surgery to the needs of the patient would mandate a more limited approach.

Facial plastic surgery practice is evolving due to patients' desire for simpler operations which are associated with a lower risk of scarring, are quicker to perform and often have a faster recovery. This has led to the introduction of less invasive techniques, such as botulinum toxin injection, application of off-the-shelf soft tissue fillers and suspension suturing, which can elevate areas of drooping. It is of note that operations on the nose have been under less competition from non-invasive techniques. A number of surgical candidates for rhinoplasty can be managed with less invasive techniques. For such individuals, adjusting the way the tip of the nose projects and achieving rotation are sufficient to provide an aesthetic and balanced surgical outcome. Indeed, if candidates are wisely chosen from amongst cases where the hump is not markedly obvious, where the base of the nose is not excessively wide or deviation of the bones too marked (in other words, where the bony part of the nose is not the main issue to be addressed), a

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_27

minor improvement in how far the tip projects and an increase in upwards rotation may still provide the desired alteration in facial appearance [2].

The outcomes in rhinoplasty are often satisfactory, but in 5–15% of cases, they are inadequate and necessitate further intervention [4–7]. Before choosing an operative approach, the surgeon needs to analyse the dimensions of the nose and how it relates to the face as a whole, as well as understanding the patient's wishes. Key principles of rhinoplasty are to aim for a harmonious outcome that is balanced, symmetrical and proportionate. The way rhinoplasty can achieve this is through alterations in relative sizes, profile, contour and overall nasal size [2].

Procedures for cosmetic rejuvenation have now moved on from merely tightening the skin, to encompass techniques that dissect and fixate tissues in a variety of anatomical planes: subcutaneous, sub-superficial muscular aponeurotic system (SMAS) and sub-periosteal [3]. Currently, the consensus is that, whatever procedure is being carried out, face-lifting should involve repositioning deeper tissues or inserting filler agents rather than simply cutting away and stretching the skin [8]. However, this is accomplished, suspending soft tissues by means of suture fixation is a vital part, and the sutures used may be either absorbable or non-absorbable [7]. Lifting skin and trimming away loose skin has been usual surgical practice for several decades; it offers a fundamental solution, albeit one which can easily lead to stigma [8, 9]. Developments in the knowledge of how tissues can most effectively be raised and an emphasis on replacing drooping structures in an anatomically superior direction have led to better cosmetic results [3]. It remains the case, however, that operative interventions still carry the risks of potential complications including infection, necrotic skin, haematoma, seroma and damaging the frontal or marginal branches of the seventh cranial nerve, not to mention the hazards of a general anaesthetic or even of an anaesthetic technique where the patient is simply sedated [10]. Facelifts still involve some visible scarring and involve a lengthy period of recovery [9–11]. Because of this, it is often the case that patients opt for less invasive solutions, in which the reduced risks of complications and shorter period of recuperation come at the price of a less radical solution to the problem [12, 13].

Using sutures to perform a facelift is not a novel approach [12, 14]. The aim is to introduce the suture underneath the facial skin and thereby lift ptotic or loose tissues, a technique which uses only small incisions and enormously shortens the period needed to recover [14]. However, whilst the non-medical press frequently writes about this technique, the surgical literature concerning how safe and effective, as well as how durable and at what risk, is notably scarce [14].

A number of materials are suitable for suture lifting, notably polytetrafluoroethylene (Gore-Tex™), polyglactin (Vicryl™) and polypropylene [14]. There are multiple ways in which the procedure is performed, but two main principles are involved at present [15]. Firstly, there is subcutaneous suspension whereby the superficial muscular aponeurotic system is used to fix the lifted tissue, which is pulled in a posterolateral direction. Secondly, there are techniques involving sub-periosteal detachment and the replacing of all the structures as one block, with lift applied only in a vertical direction [15]. The use of suspension has been broadened to include minimally invasive operations on the mid and lower third of the face. The

techniques rely on endoscopy. In this way, the soft tissues of the face can be repositioned and secured by attachment to the periosteum or fascia of the temples and only very slight incisions are called for [13].

27.2 History of the Suture Facelift

The first facelifts began over a hundred years ago. Hollander, writing in 1901[16], is usually taken as the first to describe a surgical technique that lifted facial features. In the early part of the twentieth century, other surgeons (e.g. Miller, Kolle and Lexer) varied and refined the initial technique [17–19]. The concept of dissecting under the skin in the subcutaneous plane is owed to Lexer. Before Lexer, the main idea was to cut away loose skin and achieve primary closure.

The subcutaneous dissection technique held sway right up to the first years of the 1970s. Development during these 60 years was in incisional technique, rather than fundamental principle. The situation changed with Skoog's [20] 1974 description of lifting the platysma overlying the neck and inferior face without separating the skin layer. At around the same time, the superficial musculoaponeurotic system was being described by Mitz and Peyronie, and with Skoog's innovation, this altered how many practitioners viewed face-lifting [20]. Whilst now largely superseded by newer techniques, face-lifting that involves only the skin can still be of use in certain individuals. Indeed, the ideas behind the technique are still the guiding principle for how the majority of cosmetic surgeons perform rhytidectomy [21].

Rhytidectomy that only involves lifting skin is suitable for women who are slim, whose bone structure is fine and whose skin retains its tonicity. However, if the patient has a more massive face and the underlying facial skeleton is less ideal, it will be a greater challenge to produce a natural-looking outcome, since there will be considerably more tension on the flaps of skin [22].

However, if the patient has large jowls or double chin that need correction, it may be more appropriate to employ a technique which uses suturing to lift the deeper-lying facial structures. A candidate for skin-only facelift likewise needs to appreciate that the ageing effects on other facial structures are necessarily not addressed by skin-only facelift. It is probable that skin-only facelift will become rarer as SMAS plication and purse-string suturing of the muscles beneath the skin become more and more popular [22].

27.3 Suture Lift in Rhinoplasty

Suture modification of the nasal cartilages is a fundamental technique for reshaping and repositioning them [23]. Joseph described fixing the tip of the nose to the lower septum by means of a suture [23], and since then, there have been a plethora of methods involving suturing described in the literature [23–29]. Thought suture techniques are ubiquitous; they typically complement grafts or tissue excision. Sutures are not usually considered a stand-alone method for performing a rhinoplasty.

However, this need not be the case. In carefully chosen candidates, suturing alone may be appropriate and may be performed in a clinic using local anaesthetics. Recovery time is minimal. Given the fact that the principal anatomical structures that make up the nose are unaffected, the procedure avoids key hazards, such as contour irregularities after excising the underlying lower lateral cartilages, or obstructing the internal nasal valve by trimming the upper lateral cartilages [30, 31].

Many patients have inadequate support of the nasal base and are at risk for post-operative loss of tip projection. Thus, fixation of the nasal tip has become a major goal in rhinoplasty [32, 33]. The shuttle method allows correction of mild post-surgical under-projection, without the need for a full-blown secondary rhinoplasty. Some loss of projection and rotation can occur with ageing impacting both the appearance of the nose and nasal breathing. In older patients, minimally invasive suture suspension techniques can be an effective method for restoring projection and rotation (Figs. 27.1 and 27.2).

The width of the nasal tip plays a key role in defining how harmonious a facial appearance is. The nasal tip can be narrowed slightly by suturing, since the suture goes through both lower lateral cartilages and is circular in shape. Pulling the suture tight brings the cartilages into closer apposition. In an inferior direction, the loop works just like the usual interdomal suture, with the difference that it has been placed percutaneously [2].

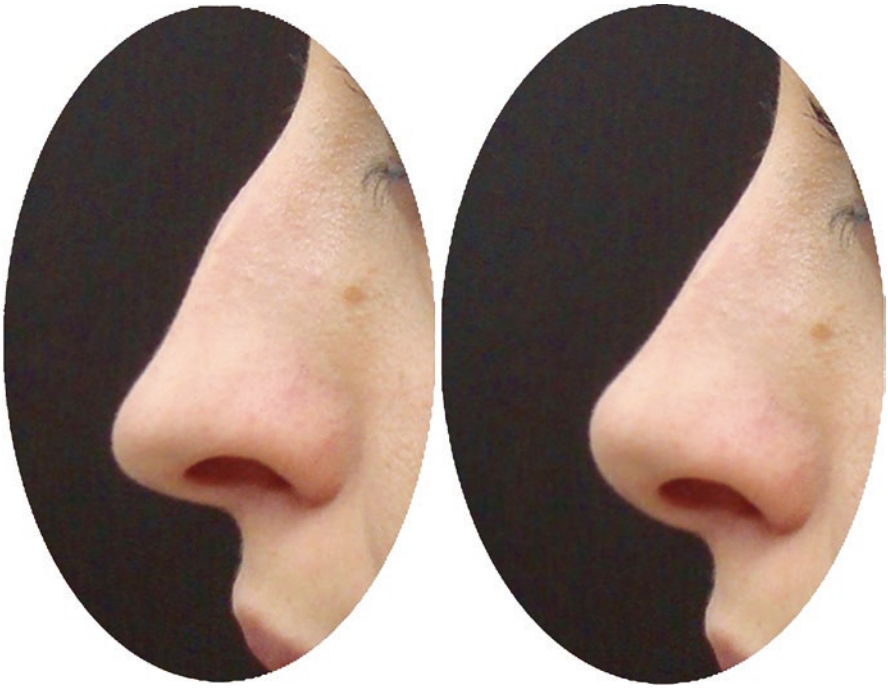

Fig. 27.1 Preoperative and post-operative views of a patient

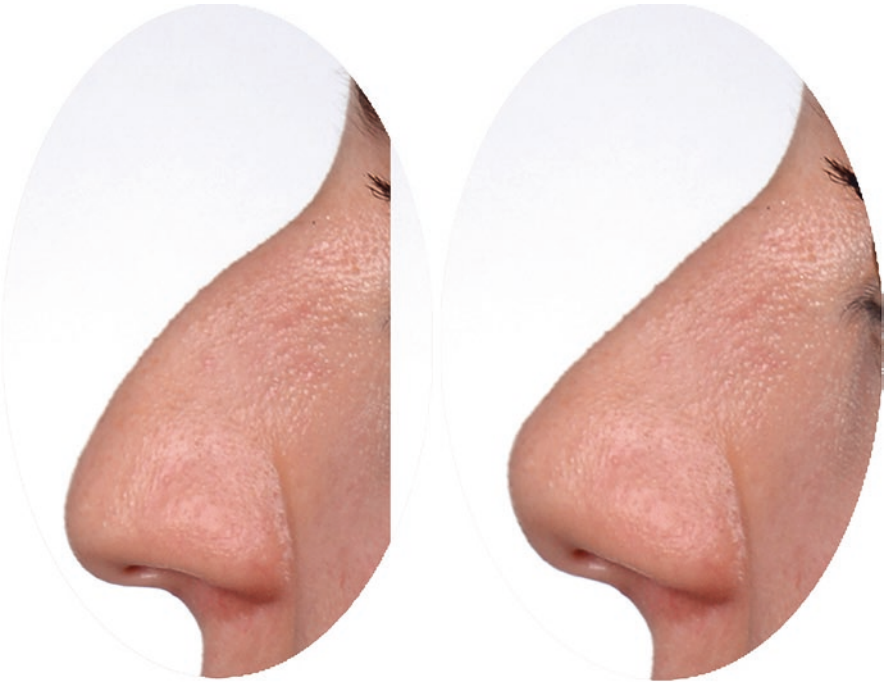

Fig. 27.2 Preoperative and post-operative views of a patient

It is more straightforward to get the appropriate amount of tip rotation if the dorsal suspension is the first suture placed, after which the septocolumellar suture can be inserted without the possibility that the columella becomes retracted. Similarly, if the tip does not project far enough, septocolumellar sutures can be sited in the septum in a more superior direction by dissecting between the medial crura in a tongue-in-groove fashion. This method is helpful in getting the tip to project an extra 1 mm or so. This may also have a beneficial effect on long-term stability. If the septal length is excessive, excision of a short length from the antero-caudal area may weaken the opposing pull created by the septal cartilage. If cephalic rotation of the lower lateral cartilages is the goal, it may be necessary to divide the scroll to permit unrestricted independent movement of the upper and lower lateral cartilages [2].

27.4 Standard Markings

Dot placement is 4 mm to the right of the nasal dorsum, just inferior to the junction of cartilage and bone at the nasal bridge; this placement is preferred as it ensures that when the transfixion suture passes through the septal cartilage, it will be forwards of the anterior nasal mucosal recess within the nasal cavity [34].

A line is then marked on the nasal lateral aspect in the direction of the most inferior portion of the columella.

This line as it goes towards the lower columella crosses the soft tissue triangle of the nostril, indicating the point where the columella would assume a different angle, in an idealised nasal form [34].

When marking the line, bear in mind the profile of the inferior lateral alar cartilages. The line should be straight and inferior [34].

In cases where the cartilages are very full and broad, let the line stray laterally towards the widest part of the nose as seen from the front. Identify the point of optimal narrowing by pressing inwards on the alar wing. This will likely be close to the dome so as not to narrow the external nasal valve. Accurate diagnosis and planning the suture placement are critical to a good outcome [34]..

A line of length 3–4 mm should be drawn on the columella along the midline to mark the point of incision, which will depend on the manner of elevating the columella.

The marking out should also be performed on the left side [34].

27.5 Technique

Ideally, a patient who is undergoing transcutaneous nasal lift will have a nose that is rather long and possesses a curvature towards the tip. The skin type should be neither thick nor sebaceous and the pores not open. The technique produces a worse outcome in individuals with a short nose or broad nostrils but is otherwise suitable for adults, regardless of age [35].

Once a suitable patient for nasal lifting is identified, preoperative photography should be undertaken. One millilitre of a local anaesthetic is infiltrated around the nasal base before incising the depressor, a further millilitre bilaterally at the osseocartilaginous junction, 1 mL nasofrontally and 2 mL on the superolateral aspect of the nose. The surgeon should incise in the inferior nasal vestibule, across the columella, to reveal the nasal depressor muscle, which is then transected, employing the Fournier technique. The tip of the nose immediately rises, but it needs to be further corrected if it is to remain elevated. Incise the nasal tip above and in front of the nasal vestibule and again incise (alternatively, two 16-gauge needles may be inserted bilaterally) in the region of the frontonasal angle, at the level of the nasal bone. The superficial tissues can be separated from the nasal cartilages by inserting a Wullstein dissector through the incision made at the tip of the nose. An 18-gauge double-pointed needle is put into the tip of the nose and passed upwards on the left side of the nose superficially to the cartilage, so that it comes out at the left nasofrontal angle. Pass a curved French eye needle from the right side of the nasofrontal angle over to the other side catching the periosteum and then thread a Prolene suture through the eye of the French eye needle and pull it across the space. Insert a double-pointed needle into the nasal tip incision and pass it along the right side superficially to the cartilage as far as the nasofrontal angle, where the suture is joined to the needle and then pulled back through the tissues, coming out at the tip of the nose.

The suture needs to be under adequate tension to elevate the tip of the nose to the desired position and then secured. Place this knot underneath the skin [2].

27.6 Conclusion

Cosmetic surgery practice is to an ever-greater extent being shaped by patients' desire for simpler operations, which are associated with a lower risk of scarring, are quicker to perform, and are where recovery is faster. A number of surgical candidates for rhinoplasty can be managed without a full classic rhinoplasty, and for such individuals, adjusting the way the tip of the nose projects and achieving rotation are sufficient to provide an aesthetic and balanced surgical outcome by sutures.

Ideally, a patient who is undergoing transcutaneous nasal lift will have a nose that is rather long and possesses a curvature towards the tip. The skin type should be neither thick nor sebaceous. It is a useful method in selected cases.

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Fillers as a New Tool for Improving Nasal Appearance

28

Müge Özçelik Korkmaz, Cemal Cingi, and Gyu Sik Jung

28.1 Introduction

As quality of life improves for people, it becomes one of their goals, whatever their age and social status, to become more beautiful. Minimally invasive procedures are growing in popularity in every area of aesthetic practice that affects the face [1]. Thread lifts and injection of neurotoxins are supplanting rhytidectomy, whilst fillers are replacing the more invasive and radical types of facial surgery that used to be popular. As well as suture lifting of the nose, every different type of filler may be tried to improve nasal aesthetics. Such interventions appear to be straightforward and swift and do not involve significant discomfort. They are often treated as though they were free of complications, despite this not being the case. The majority of ENT practitioners, as well as facial cosmetic surgeons, have begun to pivot towards such interventions. These minimally invasive aesthetic procedures have even begun to be carried out by non-medically trained personnel, such as hairdressers and beauty technicians, who now carry out injections of fillers, neurotoxins vitamins, homoeopathic solutions or plant extracts (collectively known as mesotherapy), into the face.

Indeed, a select number of surgeons are now performing filler rhinoplasty, without the use of surgery. Filler rhinoplasty refers to a procedure designed to remedy aesthetic deficits or improve the nasal profile without any cutting by the surgeon, by employing fillers of various kinds, which may be autogenous or artificial in origin

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_28

[2]. Filler rhinoplasty involving injection is suitable for the correction of an irregular profile and an asymmetrical nasal appearance.

28.2 Method

Rhinoplasty is, from a global perspective, the most frequent cosmetic procedure undertaken. In the last few years, rhinoplasty which does not involve cutting has become the first choice for the majority of cosmetic practitioners and their patients. To rectify missing volume, nasal fillers are the most frequent choice. The properties of the filler mean the surgeon can achieve an excellent outcome that is durable. Fillers formerly mostly found application as therapy for surface-related defects within the skin and were not permanent solutions. Nowadays, fillers are not employed for the removal of rhytides, but rather to replace missing nasal volume. Thus, filler injections target the deeper surgical planes, not the cutaneous layer. They are placed with surgical logic, aiming to achieve longevity of the solution.

There are five layers which compose the nasal soft tissue: the skin itself, a superficial adipose layer, a fibrous and muscular layer, a deep adipose layer and finally a periosteal or perichondrial layer [1]. Fillers are typically injected into the adipose layer, whether deep or superficial. GS Jung has detailed a technique involving injection into both layers. His recommended procedure involves simultaneous injection of filler into two discrete layers: the superficial and deep adipose tissue layers. This procedure is called the "dual-plane technique" by Jung. The filler chosen was hyaluronic acid-based, to achieve the optimal cosmetic result. Separating the filler into two sites should lessen any complications, as it means less material is deposited in one area. Both tissue compartments are bulked up, but by a lesser amount, making problems less likely [1].

It is more than a century since Corning and Gersuny operated on a patient with a saddle nose using filler. The material in use at the end of the nineteenth century was injectable paraffin. Injection of paraffin worked well at the beginning but led to grave problems later [3, 4]. Following a number of different filler types receiving marketing authorisation in the USA, there has been an upsurge in the use of fillers by surgeons to treat aesthetic problems on the nose and face. Filler rhinoplasty is part of this trend [5, 6]. Numerous fillers to go in the skin have been marketed globally from the 1980s onwards [7, 25]. The licensed indications for most such fillers are a remedy of nasolabial folds and to augment the lips. However, it has become common for the fillers to be used off-label in a number of other indications, such as tear trough correction, to make the cheeks fuller, to camouflage scarring from acne and, currently, for rhinoplasty [2].

The first use of fillers in connection with rhinoplasty was to disguise any postoperative defects or asymmetrical features. Rhinoplasty performed by surgery often produces irregular features in various portions of the nose. Several techniques were developed (both surgical and non-surgical) to remedy these defects [8, 9]. Fillers have now come to be used as a primary, rather than just secondary, treatment where the problem to be corrected is not severe.

28.2.1 Technique for the Procedure

The filler should only be injected by personnel specifically trained to perform the procedure. In particular, the following competencies are required: the ability to locate and inject within an avascular layer below the SMAS layer, i.e. just above the perichondrial or periosteal layer; remaining in the midline wherever practicable to minimise asymmetrical outcomes; aspirating to guarantee that the needle or cannula has not inadvertently entered a vessel; slow injection technique using small volumes of filler each time and reducing the number of separate places where the needle enters the skin. Using a cannula without a pointed tip may, in theory, make the procedure safer by making it less likely that a vessel has been entered [10, 11]. A bimanual approach where one hand injects whilst leaving a hand free to stabilise, pinch and mould the nose leads to a more consistent and less hazardous procedure.

Filler rhinoplasty is a fairly straightforward procedure, in which the cartilaginous and bony nasal skeleton is enhanced, little by little. Despite the simplicity of the general approach, there exist a multitude of filler rhinoplasty methods that vary in terms of filler composition, sequence of actions, way to inject, where to inject and the volume of filler to utilise [10, 12, 13].

Irrespective of the specific method followed, as long as injection is performed safely and the treatment follows a logical order in terms of nasal anatomy, the results obtainable are predictable and the procedure without undue hazard. Surgeons with experience of carrying out operative rhinoplasty find that the graft-based technique (where filler plays the role of cartilage grafts) feels familiar to them [14].

28.2.2 The Dual Plane Technique (Jung) [1]

Ten minutes prior to injecting filler, the infratrochlear nerve and the internal branch of the infraorbital nerve are blocked using 1% lidocaine with adrenalin. Initially, a filler consisting of hyaluronic acid (Teosyal PureSense Ultra Deep, Teoxane Laboratories, Switzerland), which possesses high elasticity, is injected into the deep adipose tissue layer using a 25-gauge 70 mm blunt-ended cannula. The injection enters the skin on the infratip lobule, a 25-gauge sharp-ended needle being used to pierce the skin. The cannula is pushed gradually along the deep adipose layer up to the root of the nose. Whilst propelling the cannula forward, the other hand applies gentle elevation to the skin by pinching the skin between the thumb and index finger. Once the cannula tip is at the level of the nasal root, injection of the filler can take place. The filler is deposited little by little into the deep adipose layer, withdrawing the cannula as this proceeds. The filler is deposited in the area of the nasal dorsum. Following deep injection, the same site is used to place an identical cannula in the superficial adipose layer. This time a filler consisting of hyaluronic acid (such as Teosyal PureSense Ultimate, Teoxane Laboratories, Switzerland) is placed in the superficial adipose layer. This filler possesses a mid-degree of elasticity. The same technique used with the deeply

injected filler is used, but within a more superficial surgical plane. A third cannula enters through the same hole in the skin, but this time at right angles. It is worked delicately from the tip towards the columella and the angle of the nose with the lip. When the anterior nasal spine is encountered, a hyaluronic acid filler is placed in the plane above the cartilage, little by little and with the stepwise withdrawal of the cannula. Once the cannula is withdrawn completely, no further filler is used. The volume of hyaluronic acid filler needed is between 0.4 and 1.2 mL [1].

28.3 Indications

Filler (non-operative) rhinoplasty is suitable for:

- Candidates who are not medically fit to undergo an operation.
- Candidates who do not accept the financial burden, recovery period and operative risks associated with conventional rhinoplasty.

Clinical logic dictates that suitable candidates for filler rhinoplasty will resemble those cases in which placement of cartilaginous grafts (shield, tip, radix, onlay or rim) would be part of a surgical rhinoplasty. From that standpoint, filler rhinoplasty is indicated in a number of different situations [11, 15–18].

28.4 Injection Sites

Safer injection practice depends greatly on targeting the deep adipose or sub-SMAS layer, where key vessels are not present. Injection into a vessel is potentially catastrophic as it may lead to necrotic skin or loss of vision [18]. To be able to inject safely, it is necessary to have a thorough appreciation of some terminology used in the discussion of rhinoplasty. A number of such terms are defined below:

- Anatomical dome: This refers to the most anterior area of the inferior lateral cartilages lying between the medial and lateral crura.
- Columella: The pillar separating the nostrils at the nasal base.
- Dorsum of the nose: The portion of the nose found anteriorly and bounded by the tip and the root of the nose.
- Infratip lobule: The portion of the tip bounded by the tip definition points and the junction of the columella with the lobule.
- Lower lateral cartilages (LLC): Twin cartilages at the inferior pole of the nose, composed of the medial, intermediate and lateral crura.
- Nasion: This is a region where the skin is depressed, located where the nose joins the forehead. The lowest portion of the nasion lies at a level between the eye-

lashes and the supratarsal fold, and it projects approximately 11 to 14 mm forward of the upper eyelid.

- Nasolabial angle: Imagine a line connecting the anterior to posterior points of the nostril. Then, imagine the vertical plane of the face. The angle formed between the line and the plane is the nasolabial angle, which is ideal if it ranges between 90° and 115°. Men should have a more acute angle than women to achieve the ideal.
- Root of the nose (radix): Where the nasal bones connect with the frontal bone.
- Rhinion: A point on the dorsal aspect where the bone is replaced by cartilage.
- Soft triangle: A slender fold of skin bordered by the anterior nostril, the lower domal border and between the medial crus and lateral crus.
- Subnasale: Where the columella connects to the lip.
- Supratip area: A region slightly superior to the tip of the nose. It lies in the inferior part of the dorsum of the nose.
- Tip: The point of the nasal lobule lying most anteriorly.
- Tip-defining points: The external light reflex is produced by the points on the tip which project the furthest.
- Tip projection: The degree to which the tip of the nose projects forwards, compared to the furthest point posterior formed by the junction between the nose and cheeks. A good degree of projection is between 55% and 60% of the overall nasal length.
- Tip rotation: When viewed in profile, with the base of the ala taken as the hinge point, the amount the tip moves up or down.
- Upper lateral cartilages: These twin cartilaginous structures make up the sidewalls of the mid-nasal third. They are superior to the LLC [18].

28.4.1 Augmenting the Root and Dorsum

The initial step is to decide on how high the radix and dorsum should be, plus how much supratip break is wanted (if at all). The filler is injected into the radix and dorsum in a series of drops injected at precise intervals perpendicularly to the dorsum with a 30-gauge needle. Another way to achieve this is to enter the sub-SMAS plane with a cannula and go in as far as the nasion, but no further. The bevelled cannula tip should face downwards, and the filler is injected as the needle is gradually withdrawn. For both these methods, the skin needs traction upwards to avoid the risk of blocking a vessel. Certain practitioners advocate pressure with a finger superior to the root to stop filler oozing upwards in error. Usually, 0.5 mL of filler suffices to completely augment the dorsum. Massaging the area and shaping it with the fingers assist in obtaining a regular outline. If hyaluronic acid is employed, some experts recommend the dorsum be initially overcorrected so as to allow for the swelling effect that immediately ensues upon injection. If the overcorrection is marked, shaping and massaging the dorsum is generally beneficial (Figs. 28.1, 28.2, and 28.3).

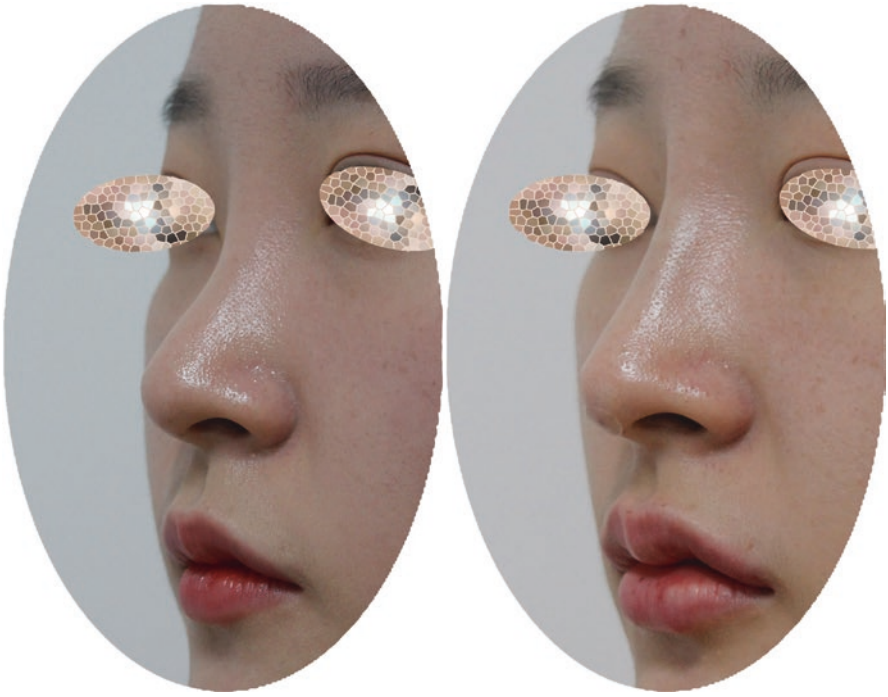

Fig. 28.1 Correction of the radix-dorsum defect with injectable filler

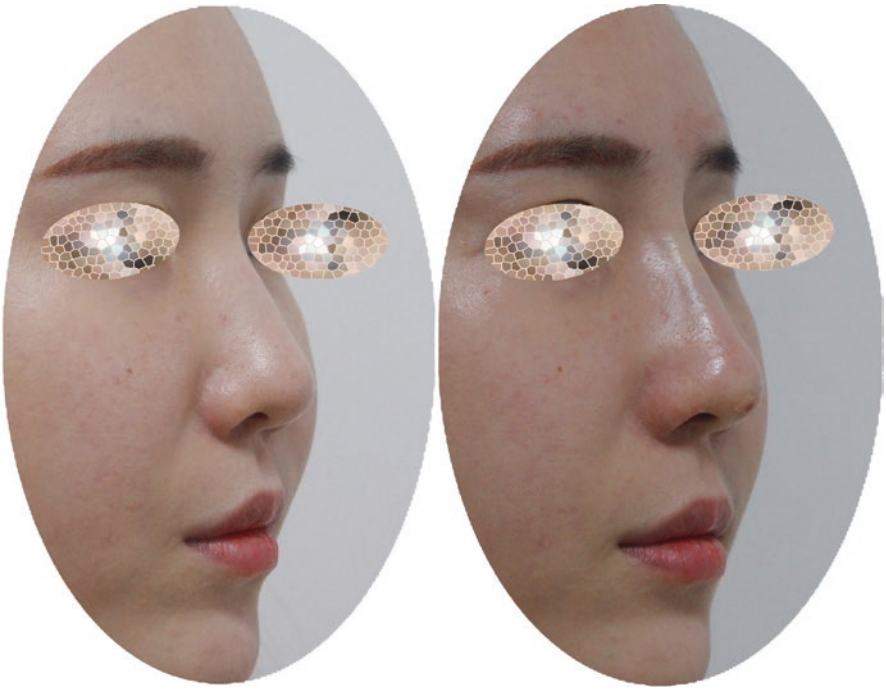

Fig. 28.2 Increasing the dorsum with injectable filler

Fig. 28.3 Correction of the dorsum defect (bone-cartilage junction) with injectable filler

28.4.2 Camouflaging a Convex Dorsum (Nasal Hump)

It is a fairly easy matter to give the illusion that a nasal hump has been reduced by injecting filler superior and inferior to the convexity, in the midline plane of the dorsum. Typically, 0.2 mL of filler is placed at each point. Before using filler, the height of the nasal root and the conformation of the supratip break need to be assessed, as when augmenting the dorsum generally [18].

28.4.3 Correcting Nasal Crookedness

Onlay grafts and spreader grafts placed asymmetrically can be used in a surgical rhinoplasty to disguise nasal crookedness. In a similar way, the filler can be placed on the dorsum or the lateral aspect of the nose to disguise a crooked outline of the mid and superior nasal thirds. However, since the vascular arcade is in the same region, particular attention is required when injecting filler laterally into the nose. Do not directly inject within the alar groove as this may lead to entering the lateral nasal artery. Indeed, certain experts advise only injecting in the midline and then shaping and massaging of the nose to squeeze the filler towards the sides, where it is needed [18].

28.4.4 Premaxillary Deficiency

Where the premaxilla lacks balance, a number of cosmetic deficits may ensue: the alar base may be asymmetrical, the tip may be different on one side, and the ala and columella may be anomalous (e.g. the ala may be retracted on one side). In an operative rhinoplasty, premaxillary grafting is possible. Analogously, the filler may be injected in this region to correct the appearance. Because of the danger of arterial embolisation, filler injection needs to be deep and approached from the medial side. It is best to use a cannula for this type of filler rhinoplasty [18].

28.4.5 Tip Projection

Just as a number of different graft types (tip, shield, caudal septal extension, amongst others) can be used to increase the amount by which the tip projects, the filler may be used to achieve similar results. The least risky way to achieve this is by injecting minute quantities of the filler where it is wished for the tip-defining point to appear. Both supra- and infratip approaches are in use, according to the practitioner's familiarity with the technique. However, the procedure is performed; filler injection should be into the perichondrial layer. Do not place the filler between the domes to avoid them separating and making the tip too wide. In cases where the infratip lobule needs to be augmented, the same effect as a shield graft can be obtained with the filler. The supratip region may be altered by injecting the filler judiciously according to where the supratip break is planned to occur. NB: the supratip invariably requires augmenting after any procedure to make the tip project further forwards. Failing to do so results in an acquired polly beak deformity [18].

28.4.6 Rotating the Tip

Rotating the tip by means of fillers is an advanced application of filler rhinoplasty and may be achieved using several different techniques. The first way to rotate the tip is actually an illusion: the nasolabial angle can be softened by a deep filler placement in the subnasale along the anterior spine of the nose, for which a 0.5 mL filler is typically adequate. A second method is to place the filler deeply in the intercolumnar space lying between the footplates of the two medial crura next to the posterior septal angle. Injecting in this area effectively works like a strut for the columella, and this makes the central leg of the Anderson tripod longer; hence, the tip projects more (and rotates) [18]. This injection technique also propels forwards the footplates of the medial crura, which is of benefit if the columella exhibits retraction. One risk, though, is that columellar show may become worse. The injected volume is generally around 0.2–0.3 mL. NB: During injection into the columella, if the columella and spine are compressed

between the fingers, the filler is kept in the midline and does not ooze towards the nasal cavity, where it may result in a blocked nose [18].

28.4.7 Contour Shaping of the Alar Rim

Just as a rim graft can correct a mildly retracted or asymmetrical ala, so can the filler injected around the rim of the ala. However, this technique may be difficult in patients who have had a surgical rhinoplasty before, since the marginal incision means that this area remains poorly supplied with blood post-surgically.

28.4.8 Functional Applications

As described above, fillers can be injected into the scroll, internal nasal valve, alar rims, and lateral walls of the nose to remedy dysfunction of the nasal valve. Fillers thereby work similarly to a variety of functional graft types (such as spreaders, alar battens, butterfly, strut or alar rim grafts) or implants (e.g. poly-L-lactate). Using fillers for functional rhinoplasty, nonetheless, is the subject of ongoing debate [18, 19].

28.5 Other Recommendations

Redaelli [1] reports on injecting hyaluronic acid at the nasofrontal angle, the nasal root and the tip defining points and claims good outcomes. There were no reports of complications arising from the employment of hyaluronic acid as a filler used in this way [20].

Hyaluronic acid is particularly useful as an add-on treatment after surgical rhinoplasty to deal with any remaining dorsal cosmetic deficits. There are concerns that using high volumes of a hyaluronic acid filler as an initial treatment for the nose may cause avascular necrosis. This is especially so if the volume exceeds 0.5 mL or the filler is composed of bigger particles, e.g. Perlane (Medicis Aesthetics, Scottsdale, Arizona, USA) or Juvéderm Ultra Plus (Allergan, Irvine, California, USA). This increase in particle size compresses the blood vessels of the nose and makes it more likely that the blood supply will be insufficient [21].

Hyaluronic acid is particularly well suited to correcting any dorsal irregularity in the vicinity of the rhinion or keystone following operative rhinoplasty. After excision of a nasal hump, the skin may thin, and callouses form after 6 months or more. These deformities appear when the swelling goes down and skin shrinks. There is evidence that a hyaluronic acid filler (i.e. Restylane) is particularly efficacious in producing a smooth outline that hides the deformity. This has given Restylane a market advantage. Experience to date suggests that a low volume of Restylane (between 0.1 and 0.2 mL) is enough for a one-off treatment of irregular dorsal

outline. This remedy appears long-lasting. One explanation for this is that the dorsum may be stimulated to lay down collagen, so that the tissue layer becomes thicker overall [20–22].

28.6 Complications

Candidates for filler rhinoplasty should be advised that, in most cases, any complications are of mild degree and will resolve spontaneously, albeit rarely there may be grave complications, of which some cannot be treated effectively (such as loss of vision or cerebrovascular accident). Complications affecting blood supply are uncommon following dermal filler use, but given the amount of dermal fillers injected, such cases will be encountered occasionally. Large volumes injected into the deep tissues to replace missing volume or fillers injected through narrow bore needles cause the most problems. Effective response to complications begins with recognising a complication has occurred and then giving hyaluronic acid, aspirin and topical nitropaste. Warm compresses should be applied and the problem region massaged. Following this first aid, persistent ischaemia may be improved by hyperbaric oxygen, which helps to save just viable tissue; the evidence base for this is slender [21–24].

28.7 Conclusion

Every intervention has its own indications and limitations. Nasal fillers may be used in limited primary deformities such as a saddle nose of minor degree or humps and slight deviations and minor dorsal problems, as well as to remedy limited postoperative contour defects. It should always be borne in mind that bolus injections and excessive interventions may produce undesired outcomes.

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What Is the Ideal Packing and Ointment after Nasal Surgery?

29

Ali Seyed Resuli, Cemal Cingi, and Jivianne T. Lee

29.1 Nasal Packing

Nasal packing is an essential component of ENT surgery. Following many different surgical procedures on the nose, e.g. rhinoplasty, septoplasty, turbinate minimization or cautery, nasal packing plays a key role in preventing haemorrhage or crust formation and, on occasion, helps secure flaps or grafts in the correct alignment. The range of products composed of various materials and marketed for use as packing has been steadily growing [1].

Nasal packing materials need to:

- Promote haemostasis following nosebleeds or an operation.
- Offer structural support to cartilage or bone, the conchae or other soft tissues (such as to an advancement flap).
- Stop adhesions forming or stenosis developing, particularly after sinus procedures. This kind of pack needs to remain in place for a more extensive period [2]. Struts [2–4] and some materials offer particular benefit in these uses.

What material a pack should be made of, the indications for placement and the duration of packing remain unresolved issues at present [6, 7].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_29

How do nasal packs work?

- Packing materials press on the tissues for haemostasis.
- They can occupy cavities to prevent adhesion formation.
- They preserve moisture by occluding the area, which then allows a return to non-pathological physiology.
- They form a barrier.
- They foster haemostasis and physiological wound repair.

29.1.1 Materials for Nasal Packs

29.1.1.1 Rubber-Covered Sponge Packs (Gummifingerlingtamponaden in German = GFT)

GFT is the name for a latex-encased sponge which is impermeable to microorganisms. Variation in the way the pack is manufactured can affect the quality of the latex and how securely thread retains the pack. An overly smooth thread runs the risk of slippage and may press unduly on the columella or the alar cartilages [1].

GFT placement is straightforward and rarely produces any injury, haemorrhage or pain. A variable pressure, ranging from slight to moderate, can be exerted on the mucosae [1].

There are, however, two important risks to consider [1]:

- The vestibulum of the nose may be traumatized, i.e. the columella and alar cartilages.
- If the pack slips backwards, there is a risk it may be aspirated.
- There is also a risk of toxic shock syndrome, if antibiotics are not prescribed prophylactically as these are nonabsorbable packs.
- These packs should be avoided in latex-allergic patients.

29.1.1.2 Expandable Nasal Packs

Expandable nasal packs are manufactured from the material polyvinyl acetate, viscose and cellulose (Sugomed) [1].

29.1.1.3 PVA Nasal Packs (=PVA-NP)

PVA nasal packs start off small in size and are available as several different types of different dimensions. The glue dissolves when it touches blood or water, allowing the pack to decompress and increase in size. The absorption capacity of the packs is 20 times their original weight. The material is soft and springy, so that a slight or medium pressure can be applied to the lining of the nose. How smooth and what size it is decide how easily a pack can move. A very small pore size means that granulation tissue does not spread into the pack itself, and that means a smoother pack will be easier to remove without causing pain or bleeding. Small pore size also results in a denser pack and one which better resists stretching. Liquids are absorbed more gradually, and less liquid is taken up by the pack. The most well-known PVA-NP is

Merocel. The big pore size of this material, nonetheless, means that it and similar products are unsuitable for nasal packing [1].

An ideal PVA-NP:

- Has minimal pore size, making it more comfortable to remove (3.08 versus 5 on a VAS 0–10, series 5000) [8].
- Has a coating on the sides (like Merocel Laminated) consisting of a composite material, which decreases tissue injury still more. The front, back, top and bottom of the pack need a rough surface with large pores.
- Should possess antimicrobial activity against *Escherichia coli*, staphylococci, *Yersinia* spp., *Serratia* spp. and *Bacillus subtilis* [1].

29.1.1.4 Sugomed

Sugomed comes in strip or plate form and is capable of expansion. It is composed of cellulose (31.3%) and viscose (68.7%). Liquids are absorbed, making the material swell, albeit not as much as PVA-NP. The pores are finer than the original Merocel, which increases patient comfort when taking the pack away, but packs with a smoother surface are still superior in this regard. The principal reason to prefer Sugomed over Merocel is that the packs can be personalised in terms of dimensions and form. Some surgeons use one long strip to go inside both nostrils. Doing this carries the risk of putting pressure on the columella [1].

29.1.1.5 Rapid Rhino

Rapid Rhino refers to a nose pack, the inside of which is spongy. Several types exist, e.g. Riemann, Goodman or Mannheim, and length varies. There also exists a balloon coated with carboxymethyl cellulose (CMC). CMC coats both parts, i.e. the balloon catheter and the spongy inner layer. The pack exerts pressure and closes gaps in the nasal cavity. Thus, it is a kind of formed nasal pack. Whilst it is known that platelets aggregate in response to CMC, which has beneficial haemostatic effects, this is probably only a minor part of how the pack works. When CMC is mixed with water (not saline, however), a gel results which has a smooth consistency and is beneficial in membranous recovery. This is a key part of how the pack with a spongy inner layer functions, but it is probably a minor element in how the balloon catheter-type pack achieves its benefit. The packs have nylon threads sewn into them, and this may stick to the mucosa and prevent the pack from being easily taken out. The benefits of the gel, i.e. occlusion of injury and restoration of physiological homeostasis, are available separately as CMC. This is sold as a Sinu-Knit or Stammberger gel [1].

Rapid Rhino has been shown to offer superior patient comfort, defined as pain whilst being put in place and taken out, or nosebleed [9, 10]. Rapid Rhino is also effective in individuals with a nosebleed or following sinus operations [9–12].

29.1.1.6 Cotton Gauze Strips

Cotton gauze strips vary in terms of how wide they are, the calibre of the knit and what type of threads are integral [1].

29.1.1.7 Balloon Packs/Balloon Catheter

Possibly the only reason to use balloon packs is for a grave nosebleed originating in the posterior nasal cavity. They are effective and swift in this indication. Whilst balloon packs do not occlude the branches of the sphenopalatine artery in a direct fashion, they can isolate the nasopharynx. Once the front of the nasal cavity has been blocked off, the rest of the cavity can be pressurised to put pressure on the leaking blood vessels. The most basic balloon packs use a single balloon. Others have twin balloons to place within the nasal cavity and the nasopharynx. Twin catheters do, however, carry the following risks [1]:

- The anterior balloon puts pressure on the nasal septum and turbinates and may cause necrosis, rather than directly compressing the leaking arteries. The balloon pushes the septum over to the other side [13]. In a case where the anterior balloon is directly compressing a bleeding vessel, a similar therapeutic effect can be achieved with diathermy or a less invasive placement of nasal packing.
- The vestibulum of the nose is prone to injury, particularly if the catheter is too short. This means long packs are needed each time.
- It is not generally necessary to undertake sinus surgery unless the posterior plate of the maxillary sinus is hard to find.
- Many arterial branches may exist [14].
- Simmen states that the branch of the artery supplying the anterior plate of the sphenoid sinus is the most commonly affected.

Balloon packs possess a greater degree of sophistication than Foley catheters, but the latter can achieve the same result at a lower cost. All balloon packs suffer from problems in securely attaching the catheter. Necrosis of the ala is also a problem. Several suggestions have been offered as to how this danger can be minimized:

- Secure the nasal pack anteriorly with a very secure knot.
- Coat the surface with foam [15].
- The distal end is cut and positioned 8 cm further than the proximal end of the dilated balloon and clamped into place [16].

29.1.1.8 Hemostatic/Resorbable/Biodegradable Packs

Patients now expect to be more comfortable following sinus operations than was previously the case. Some ENT clinicians have made the decision not to use nasal packs at all, since they carry several risks. Novel products have come into the market to fill this gap, but these products cannot press nor support, as conventional nasal packs used to do. The older products had the following drawbacks [1]:

- The pack exerts pressure when in place that can damage the cilia of the mucosa. This may also occur due to injury when placing or taking out a pack.
- Taking away the pack can cause injury and haemorrhage.
- Packs may be uncomfortable because of the pressure they exert.
- There are other, more detailed risks.

In nasal septal operations, nasal packs are unnecessary provided specific suture techniques and splints are employed. In contemporary operations on the sinuses and conchae (done endoscopically), nasal packs are frequently unnecessary. However, aggressive conchal reduction or radical sinus surgery frequently results in profuse bleeding that calls for formed packs, as formed packs are the only means by which adequate pressure can be applied. Using more gentle endoscopic sinus surgical techniques not only offers comparable or superior outcomes from the operation but also lessens the disadvantages, such as crusting, scar or bone spur formation after injury trauma. As a final note, more comfortable nasal packs can be utilised [1].

Combining materials in various ways can achieve a variety of aims [1]:

- Haemostasis.
- Taking advantage of adhesive quality to position tissues.
- Barrier formation.
- Better recovery from trauma.
- Ability to seal a surface or cavity.

29.1.1.9 Gelatine (Gelfilm, Gelfoam)

Researchers in the US report on the application of gelatine obtained from porcine skin to the osteomeatal unit or ethmoid following sinus operations. This was carried out as well as positioning a nasal pack. When this material was applied in the sinuses, scar formation increased, adhesions were formed, and the maxillary meatus narrowed [17–19].

29.1.1.10 Bovine Gelatine Plus Thrombin (Floseal)

Floseal gel possesses high viscosity and aids in haemostasis. It can stick even to rough or wet surfaces like those in the nasal sinuses, even if the haemorrhage is extensive [20]. It may be employed in individuals with platelet deficiency or with abnormal platelet activity. Floseal is the highest rated haemostatic pack [5, 21]. Nonetheless, there are also several disadvantages:

- Scarring and adhesion formation is more common [22–26].
- Foreign body reaction may occur, and the foreign body may become integrated into the mucosa, even where no injury was present [25, 26].

29.1.1.11 Hyaluronic Acid (I.E. Merogel (Esterified Hyaluronic Acid), Sepragel (Hyaluronic Acid Polymers with Cross-Linkage), Seprapack (CMC in Combination with Hyaluronic Acid))

Hyaluronic acid (HA) occurs naturally as an unbranched polysaccharide (glycoamino-glycane) consisting of repeating disaccharide units of sodium-d-glucuronate and N-acetyl-d-glucosamine. It is located in the basal membranes of cells and soft tissues. It plays a key role in cellular increase and migration. HA is a vital element in the repair of injury in the foetus, a process with virtually absent scar formation [1].

29.1.1.12 Other Hemostatic Materials

Fibrin adhesive has been employed in nosebleeds, coagulopathies, nasal septoplasty and sinus operations [27]. This adhesive has lower associated oedema, crusting and atrophic cicatrification than diathermy, silver nitrate application or nasal packing, when used to manage nosebleeds. At present, its role in sinus surgery has not been fully evaluated.

29.2 Ointments on Nasal Packs

Typically, surgeons employ vaseline or antibiotic ointments. Ointments allow for frictionless insertion of strips and the prevention of crusting. It is assumed that antibiotics stop infections, although this has not yet been experimentally confirmed. Cotton gauze strips should not be utilized post-surgically on the septum, conchae or sinuses as they are not very effective [1].

Ointments may be mixed according to the clinician's inclination, before application to nasal packs.

One possible combination is ciprofloxacin, ketoprofen, ephedrine hydrochloride and lanolin, which has the following advantages:

29.2.1 Ciprofloxacin

Topical preparations have the benefits of delivering the agent precisely to the lesion and achieving a high localised bioavailability without a correspondingly high systemic concentration. Drawbacks are that it may be difficult to apply to the lesion, there may be localised side effects, such as nosebleed or pain, and entry into the sinuses may be hit-and-miss. However, as the nasal cavity and sinuses are generally straightforward to access, this is a popular site for topical treatments and topical preparations are now integrated into the treatment of chronic rhinosinusitis, for example. Oral ciprofloxacin has been shown to achieve a higher concentration in the mucosa than a topical ointment in patients with chronic rhinosinusitis, but at the cost of a high plasma concentration, and gel was seen to be the best form for a topical preparation of ciprofloxacin [28].

29.2.2 Ketoprofen

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) and its mechanism of action is the inhibition of the cyclo-oxygenase enzyme, which is a key enzyme in the synthesis of the prostaglandins. Prostaglandins are pro-inflammatory modulators. Inhibition of prostaglandin synthesis has the effect of dampening down the inflammatory response. Topical ketoprofen has been employed as analgesia and anti-inflammatory in the following conditions: minor bruising injuries, tendonitis, osteoarthritis of distal joints, acute lumbar pain and phlebitis [29].

Topical ketoprofen preparations exist as creams, gels, solutions, sprays and plasters, with a variety of proprietary as well as generic products on the market [29]. The rationale for the inclusion of ketoprofen in an ointment for nasal application is to shorten the duration of wound healing.

29.2.3 Ephedrine Hydrochloride

Nasal blockage resulting from several different disorders that affect the nose is commonly managed through the use of nonselective adrenergic alpha-agonists, e.g. phenylpropanolamine and d-pseudoephedrine [30]. Since both ephedrine and pseudoephedrine cause vasoconstriction to the lining of the nose, they are very suitable to prevent nasal congestion from developing [31].

How the plexus of vessels which supply the mucosal lining of the nose is regulated has a profound effect on the engorgement of blood in the venous sinuses, which then causes mucosal swelling, leading to the lower flow of air through the nose. Thus, any disturbance here leads to a perception of nasal stuffiness [10]. Both the venous and arterial sides of the vascular network are innervated by adrenergic fibres acting on alpha- (vasoconstrictive) and beta- (vasodilatory) receptors. The alpha-receptors are more preponderant [10]. Ephedrine and pseudoephedrine act on the vascular plexus via alpha-receptors to produce vasoconstriction and hence relief of nasal blockage. This improves the patient's quality of life.

29.2.4 Lanolin

Lanolin has benefits as it produces a frictionless surface and stops adhesions to the pack from forming.

Lanolin itself is a light yellow-coloured, sticky liquid which is extracted from sheep's wool. Melting lanolin gives it a non-cloudy yellow-tinged appearance. Although lanolin is sometimes referred to as wool fat or wool grease, since it does not contain glycerides, chemically speaking, it is not a fat. The main components are sterol esters; thus, it is more appropriately termed a wax [32]. Lanolin forms a physical barrier to adhesion to make packing easier to take out later. It must be avoided in lanolin allergic patients.

29.3 Conclusion

An ideal nasal packing material should possess the strength to keep the bones, septum and mucosal flaps in the desired position. It should compress vessels and thus staunch haemorrhage yet be sufficiently gentle to avoid irritation and patient discomfort whilst in place.

Any ointment over the pack serves to counter infection, oedema and crusting. If the ointment has a greasy quality, it will act as a lubricant for the insertion and removal of the nasal pack, rendering its use easier for both the surgeon and the patient.

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The Best Time to Operate on Nasal Polyps

30

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30.1 Introduction

A general definition of a nasal polyp is that it is an inflammatory-based pathological outgrowth of any part of the mucosal lining of the nose or paranasal sinuses. Several pathological processes terminate in polyp formation. The polyps most frequently reported on are non-malignant, translucent lesions within the nose that originate from the nasal lining or at least one of the paranasal sinuses, especially in the path of sinusal drainage [1].

Children afflicted with persistent sinusitis, allergic rhinitis, cystic fibrosis (CF) or allergic fungal rhinosinusitis (AFRS) may have a number of such polyps. A singly occurring polyp may represent an antral-choanal polyp, a benign massive polyp or any neoplasm (whether malignant or not), such as a glioma, haemangioma, papilloma, juvenile nasopharyngeal angiofibroma, rhabdomyosarcoma, lymphoma, neuroblastoma, sarcoma, chordoma, nasopharyngeal carcinoma or inverted papilloma. Encephalocoeles may also mimic nasal masses. Any child who presents with benign-appearing sinonasal polyposis should be evaluated for CF or asthma. It is essential for patients to be aware that polyps tend to recur and that the problem may well persist [1]. Indeed, up to 80% of patients may experience polyp recurrence within 40 months of endoscopic sinus surgery [2].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_30

30.2 Pathophysiology

The precise aetiology of polyp formation in the nose is not known. Links have, however, been established with persistent inflammation, autonomic systemic disequilibrium and genetic factors. The majority of explanations for polyp formation cite persistent inflammatory processes as a major element; hence, those disorders characterised by chronic inflammation tend to result in polyposis.

Multiple non-malignant polyp formation occurs in the following disorders [1]:

- Asthma. 20–50% of cases of polyposis are asthmatic.
- Cystic fibrosis (CF). Polyps occur in between 6 and 44% of cases of CF [3].
- Allergic rhinitis.
- Allergic fungal rhinosinusitis (AFRS). Polyps occur in 85% of cases of AFRS.
- Chronic rhinosinusitis (CRS).
- Primary ciliary dyskinesia.
- Aspirin-exacerbated respiratory disease. 8–26% of cases of polyposis are aspirin intolerant.
- Alcohol intolerance. 50% of cases of polyposis are alcohol intolerant.
- Eosinophilic granulomatosis with polyangiitis (EGPA). Polyps occur in 50% of cases of EGPA.
- Sinusitis-infertility syndrome (persistent sinusitis, nasal polyp formation, azoospermia).
- Nonallergic rhinitis with eosinophilia syndrome (NARES). Polyps occur in 20% of cases of NARES.

It seems that the development of polyposis is linked in the first place to chronic inflammation, of whatever cause. Paediatric cases of persistent sinusitis, allergic rhinitis, CF or AFRS are all associated with polyposis. Where polyps occur singly, the lesion may be an antrochoanal polyp, a giant non-malignant polyp or a cyst within the nasolacrimal duct. A more complete list of possibilities is given below. Note that some of these lesions are congenital, and others are neoplastic (both malignant and benign) [1]:

- Cyst within the nasolacrimal duct
- Encephalocoele
- Glioma
- Dermoid tumour
- Haemangioma
- Papilloma
- Juvenile nasopharyngeal angiofibroma
- Rhabdomyosarcoma
- Lymphoma
- Neuroblastoma
- Sarcoma
- Chordoma

- Nasopharyngeal carcinoma
- Inverted papilloma

30.3 Objectives of Therapy

For the majority of cases of CRS, a cure remains elusive. Treatment is therefore palliative, aiming for better quality of life. Treatment objectives include the following [4]:

- Management of inflammation and oedema within the mucosa.
- Preserving aeration of the sinuses and ensuring clear drainage.
- Eradication of colonisation or infection by microbes, where it occurs.
- Lessening the frequency of attacks.

Treatment of CRS follows a pattern that will be familiar from treating asthma: first, therapy is optimised for reduction of symptoms; then, maintenance regimes are instituted, with provision for observing the effect over time and adjusting to manage any attacks that do occur. The phenomenon of remodelling of the mucosa has become the subject of a research effort seeking to establish the reasons for the refractive nature of persistent CRS. Such remodelling is thought to feature in asthma. How far therapy can retard or stop remodelling is still unknown [5]. The fact that pharmacological strategies to manage CRS also lessen asthma symptoms is further evidence that the pathophysiology of asthma and CRS has many common features [6].

30.4 Medical Care

The principal pharmacological treatment for nasal polyps is corticosteroid therapy, both systemic and intranasal [7–9]. There is minimal advantage in the use of histamine blockers, decongestants or cromolyn. Allergic rhinitis may be successfully treated using immunotherapy, but this typically fails to cause pre-existing polyps to regress. Where bacterial infection has supervened, the use of antibiotics is recommended [1].

Steroid therapy is therefore the first-line treatment, and it should be oral or intranasal. Steroidal injection in the polyp base is not FDA-approved (in the United States), due to the reported loss of vision that occurred in three individuals treated in this way with Kenalog®. However, the risk may depend on the size of the particular preparation of triamcinolone. Aristocort® has a larger particle size and thus a lower likelihood of entering the cranium. It is vital to ensure such injections do not penetrate into a blood vessel.

The treatment with the highest efficacy on nasal polyposis is systemic steroid treatment. Most reports recommend the use of oral prednisolone at a dose of between 30 and 60 mg for 4–7 days, followed by a reducing dose over one to 3 weeks.

Paediatric dosages are variable; however, a dose greater than 1 mg/kg/day is seldom needed. The course usually lasts 5–7 days and is then reduced over a 1- to 3-week interval. Treatment response to steroids seems to be linked to whether eosinophilia occurs. Individuals with polyposis and conditions linked to eosinophilia, such as allergic rhinitis and asthma, usually respond more readily [1].

Conversely, if the polyps are not in association with eosinophilia (such as occurs in CF, primary ciliary dyskinesia syndrome or Young's syndrome), corticosteroid treatment may lack efficacy. Long-term corticosteroid treatment carries a number of adverse effects, including retarded growth, diabetes mellitus, hypertension, psychiatric effects, damage to the gut, cataract formation, glaucoma, osteoporosis and aseptic necrosis of the head of the femur. Multiple reports suggest corticosteroids be given intranasally in polyposis, either as initial therapy or as maintenance therapy following systemic steroid use or surgical operation. The majority of intranasal steroid preparations (such as fluticasone, beclometasone and budesonide) both provide symptomatic relief and can be shown to ameliorate airflow through the nose in objective trials (especially in placebo-controlled studies featuring blinding) [10].

30.5 Operative Care

In paediatric cases of numerous, non-malignant polyps, or CRS, where pharmacological treatment at full dose has not brought relief, an operation is needed. Polypectomy alone works as a first stage in resolving nose-related symptoms, particularly if there is a sole polyp or polyps are few in number (see the illustration below). However, polyp excision suffers from a high level of recurrence when the polyps are both numerous and benign [1].

Endoscopic sinus surgery (ESS) is superior to conventional methods insofar as it both allows polypectomy and opens the middle meatal clefts (the typical area of formation). Recurrence after ESS is therefore lower. How extensive the operation should be is unclear due to a lack of specific research on the subject. Possibilities range from total removal to improving the ventilation of the sinuses. Complete removal does appear at least as good or better than improving ventilation, in what little research is available. In the hands of an experienced surgeon, complications are rare. Surgical microdebriders allow for swifter and less risky surgery, since they allow greater precision in incision and reduce blood loss, alongside providing a better view for the surgeon [1].

The operation targets affected areas seen on CT imaging preoperatively. Certain conditions warrant surgery as first-line treatment, since steroid therapy is largely ineffective. Such conditions include CF, primary ciliary dyskinesia syndrome and Young's syndrome. Following the removal of the lesions, the respiratory tract usually begins to recover.

Intraoperative image guidance may be beneficial, since key landmarks to identify the nasal, sinusal, orbital and intracranial anatomy relevant to polypectomy or revision operations may have been changed unrecognisably [1].

Between 6 and 48% of paediatric CF cases have polyps within the nose. Operative intervention is indicated once symptoms appear. Virtually, all such cases result in repeat procedures at intervals of a few years, since the polyposis keeps recurring. Many of the conditions that are associated with polyposis do in fact recur, so patients should be advised accordingly before any procedure [1].

30.5.1 Indications for Sinus Surgery

CRS involves the mucosal surfaces of the sinuses and nasal cavity becoming inflamed. Cases of CRS and healthy controls have the same rate of the anatomical anomaly (e.g. deviated septum) [11], so operative intervention should not be the first step for most individuals with CRS. A few cases of AFRS may warrant surgery as the first-line therapy, however.

Functional ESS may be used to reopen the drainage pathways and allow the sinuses to receive a normal level of ventilation. This then allows the inflammatory process to recede gradually. Given that functional ESS has no direct effect on the inflammation itself, pharmacological treatment of the inflammation is needed if the symptoms are not to recur [12]. Operative polypectomy is especially prone to recurrence, and polyposis generally recurs in the space of a few years unless pharmacological treatment for maintenance is instituted [12, 13].

The reasons to undertake an operation are as follows [4]:

- To allow proper ventilation of the sinuses to take place. The ostia are rendered patent, and opacified sinuses are cleared of extraneous material.
- Marked polyposis may be debulked.
- Pharmacological therapy at high doses has been a failure.
- The osteal tissues are eroded, or the lesion has spread outside the sinus.

Some evidence points to the superiority in the long term of pharmacological treatment over surgery in cases where asthma and CRS coexist [6, 14].

30.5.2 Endoscopic Surgery

FESS was the subject of a systematic review in 2006. The authors report that the technique had acceptable safety but failed to find the superiority of FESS (as the authors defined it) over pharmacological therapy [15]. One limitation is that only three RCTs were available to inform the review.

An especially thorough study looked at the outcome measures of 120 cases seen consecutively and followed up for an average of a year and a half [16]. Almost the entire cohort stated that the symptoms of CRS had improved when they were seen for the last follow-up. About 85% described marked and 13% mild improvement. Only 2% did not report improvement. Despite these outcomes, endoscopy revealed sinus cavity abnormality in 45% of cases when the trial came

to an end. Having advanced features of polyposis prior to surgery was associated with a greatly elevated risk of recurrence post-operatively. A subsequent study included 72 cases from the earlier study, and they were seen on average 7.8 years later. Of the 72 patients, 98% had improved symptoms, but it is unclear how much weight to attach to this finding, since the other cases from the original study were not followed up [17].

More recent analysis of a UK cohort suggests that earlier surgical intervention was associated with less post-operative health care use [18].

30.5.3 Sinus Ostial Dilation (Balloon Ostial Dilation)

Balloon ostial dilation (BOD) refers to an operation used to enlarge the ostia of the frontal, sphenoid or maxillary sinuses or to displace the ethmoidal infundibulum. BOD has also been referred to as "balloon catheter sinusotomy", and there are other terms in use. However, "balloon ostial dilation" is the term preferred by the American Academy of Otolaryngology-Head and Neck Surgery [19]. BOD does not result in any operative tissue excision, and the procedure is therefore suitable for use in an outpatient clinic, with local anaesthesia only. To enlarge the ostia of the maxillary sinus, the balloon catheter must be placed in the maxillary sinus through the natural ostium, behind the uncinate process. Head-to-head trials comparing BOD and functional ESS are lacking, making a comparison of outcomes difficult to assess. Furthermore, what evidence exists has mostly been gathered from research sponsored by balloon catheter companies [4]:

- A systematic review dating from 2011 that assessed the role of BOD in the management of CRS found a single research trial involving 34 cases that met the criteria to be included. The conclusion reached by the authors was that there is no solid evidence on which to recommend BOD above conventional operative techniques in cases where CRS has not responded to pharmacological measures [19].
- A case series that observed individuals undergoing BOD noted that at least 85% of cases were successful and fewer than 10% of cases needed a revision procedure. The follow-up lasted 6 months [20] or 2 years [21].
- After these studies, a trial employing randomisation, but with open label and sponsored by the manufacturer, was carried out with 92 individuals. All had straightforward CRS of the maxillary sinus +/− pathology of the anterior ethmoid. They were allocated to outpatient BOD or functional ESS [22]. Exclusion criteria included massive polyposis, AFRS, aspirin-exacerbated respiratory disease (AERD), having undergone a prior operation, or other complications. The main outcome measures were improvement in Sino-Nasal Outcome Test-20 (SNOT-20) scores after 6 months and whether debridement was required following the procedure. For both the BOD and functional ESS cases, clinical benefit was noted on SNOT-20 (−1.67 with BOD, and −1.6 with Functional ESS. A

score of −0.8 was considered to show clinical significance). BOD was superior in terms of having a lower frequency of postsurgical debridement to resolve clots, scabbing, crusting and synechial formation than functional ESS. This difference reached the level of statistical significance. In this way, the non-inferiority of BOD was demonstrated in a subgroup of individuals with straightforward CRS. At 1 year, the improvement was maintained [23].

30.5.4 Medical Adjuncts to Sinus Surgery

A number of adjunctive medical treatments now exist alongside sinus surgery.

30.5.4.1 Glucocorticoid-Eluting Sinus Implants

The FDA has granted approval for the use of implants which elute mometasone to preserve the ostia of the ethmoid or frontal sinuses in a patent condition after ESS [24, 25]. These implants elute 370 μg mometasone furoate within a 30-day period. They consist of a biodegradable matrix that can be absorbed by the body. A number of trials plus one meta-analysis have addressed the benefit from these implants [26–30]. The meta-analysis involved 2 RCTs and 143 cases altogether. Devices that elute a medication were compared with non-active implants. Postsurgical intervention fell by 35%, the need to separate adhesions fell by 51%, and the use of corticosteroids by mouth fell by 40% when the drug-eluting implants were used [29]. A different trial showed the efficacy of the devices in recurrent polyp formation after ESS. The device was implanted in the ethmoid space as an outpatient procedure. The results showed that polyps reduced in bulk, the ethmoid sinus patency was improved, and nasal stuffiness was better at 6 months' follow-up [31].

30.5.4.2 Glucocorticoid-Impregnated Nasal Dressing

It is also possible to provide topical corticosteroid treatment by the use of a dressing soaked in corticosteroid. The evidence base for this practice is less well developed. One retrospective study looked at 21 cases, which were matched with controls. The 21 subjects had absorbable nasal dressings containing 20 mg of triamcinolone placed in the middle meatus [32]. Frank polyposis was an exclusion criterion. The benefits at 4 and 8 weeks were comparable to the control cases where methylprednisolone by mouth had been provided. The controls received methylprednisolone 24 mg stat, with a reducing dose staggered over 6 days, and then stopped. This trial indicates an alternative way of providing intranasal topical steroids, with the advantage that the local concentration is high but systemic levels of steroid low. The procedure can only be done by an ENT specialist. There is a need for more research to clarify how dosage can be optimised, how long benefits persist and which cases are most suitable. A different study utilised dressings dosed with triamcinolone 20 mg, supplied to each side of the nose. This equates to prednisolone 17 mg o.d. by mouth. There was suppression of systemic cortisol initially (day 2) but recovery by the tenth day [33].

30.5.4.3 Macrolide Antibiotics

Some research has looked at potential benefit from macrolide antibiotic therapy after surgery on the sinuses undertaken to improve various kinds of CRS [34, 35]. Although a systematic review produced in 2017 did identify evidence of benefit from using macrolide antibiotics post-surgically in cases of CRS with nasal polyp formation, the evidence was felt to be low in quality [36]. Hence, the use of antibiotics in this way is not recommended.

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Surgical Treatment for Inferior Turbinate Hypertrophy

31

Zeynep Önerci Altunay, Hüsamettin Yaşar, and Peter Catalano

31.1 Introduction

The inferior turbinates (IT) are very important for the regulation of nasal airflow and normal respiratory function. The anterior part of the ITs plays a role in nasal physiology. The resection of any part of the IT should be avoided.

IT hypertrophy is important in nasal stuffiness. The underlying etiology of IT hypertrophy should be investigated before doing any surgical intervention [1]. Allergy testing should be performed, and any allergies should be treated (Fig. 31.1). Septal deviation may cause compensatory hypertrophy (Fig. 31.2), typically on the convex side of the septal deflection. After septal deviation correction, compensatory inferior turbinate hypertrophy should be addressed as well.

Rhinosinusitis is another important cause of inferior turbinate hypertrophy. The presence of any inflammation in the sinuses should be investigated before any surgical intervention and should be treated. If endoscopic surgery is needed, it can be done in the same session with IT surgery.

The IT is formed by the bone, submucosal tissue, and the overlying mucosa. To decide the type of IT surgery, an understanding of the contributing component of the inferior turbinate hypertrophy is important [2]. CT scan is also helpful to understand the type of inferior turbinate hypertrophy. It should be known whether it is mainly bony, or mucosal hypertrophy, or mixed. Any inferior turbinate abnormality such as IT concha bullosa or a benign tumor, such as fibrous dysplasia, can be assessed on CT. On CT scan, the attachment of the IT and its angle with the lateral bone should

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_31

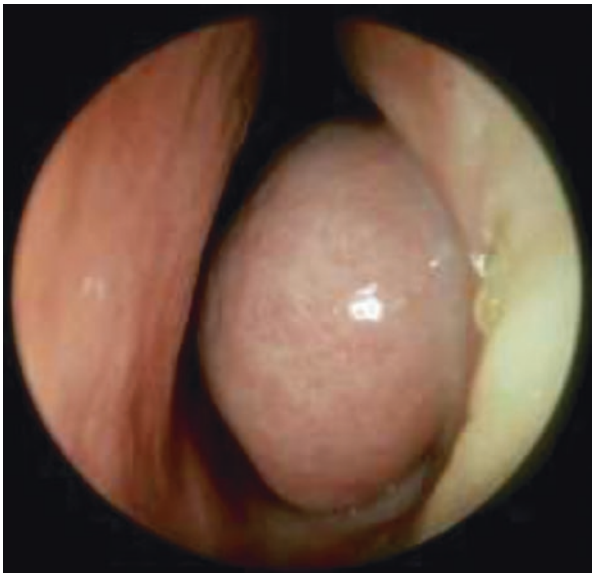

Fig. 31.1 Left IT hypertrophy due to allergic rhinitis. Notice the pale and swollen inferior turbinate with watery secretion (Courtesy of TESAV)

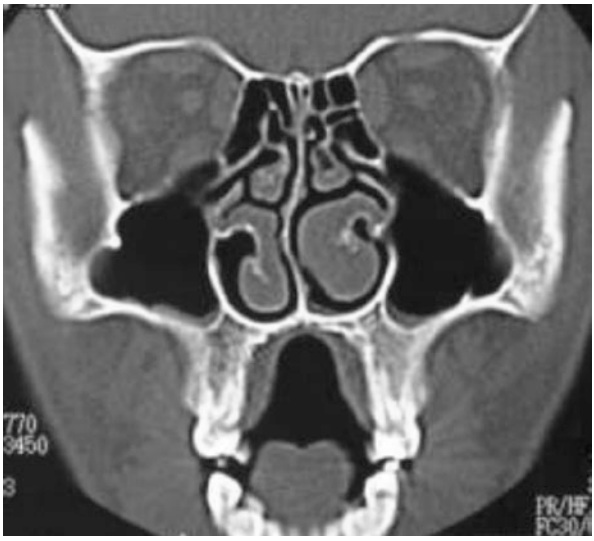

Fig. 31.2 Septal deviation to the right and compensatory left inferior turbinate hypertrophy (Courtesy of TESAV)

be assessed. This angle is important since if the angle is 90°, in other words at the right angle to the lateral nasal wall, simple outfracture will cause only the fracture of the descending part of the IT and the symptoms will recur a few months later [3] (Figs. 31.2 and 31.3).

Various medical and surgical treatment modalities have been advocated for IT hypertrophy. The main purpose is to reduce the size of the IT. Antihistamines, intranasal corticosteroid sprays, decongestants, or oral corticosteroids can be helpful, especially in allergic rhinitis patients. When they do not succeed, surgical techniques are used [4].

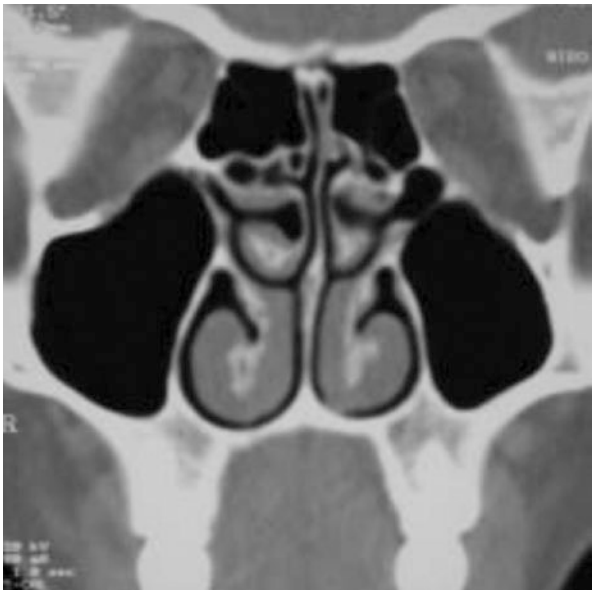

Fig. 31.3 The inferior turbinate angle is different from the one in Fig. 31.2 (Courtesy of TESAV)

31.2 Surgical Techniques

31.2.1 Mucosa Preserving Techniques

31.2.1.1 Inferior Turbinate Lateralization

The IT bone attaches laterally to the maxillary and palatine bones. The best procedure for decreasing the angle at the IT bone attachment site with a lateral nasal wall is lateralization of IT bone. With a blunt instrument, it is first infractured medially and superiorly to fracture the IT bone at its junction with the lateral nasal wall. Then, it is outfractured laterally and inferiorly. This surgery does not decrease the turbinate size, and if not combined with turbinate reducing techniques, the benefit is limited (Fig. 31.4) [5]. Lee et al. reported that the bony IT and its overlying compensatory soft tissue hypertrophy remain lateralized 6 months after outfracture [6]. For the success of lateralization surgery, the angle of the IT attachment with the lateral nasal wall is important. If this angle is 90°, then the bony attachment should be cut or fractured from the lateral nasal wall with osteotomes or chisels as described by Legler (Figs. 31.2, 31.3, and 31.5) [7].

31.2.1.2 Submucosal Electrocautery

Monopolar and bipolar electrocautery can reduce the turbinate hypertrophy. The needle electrode is inserted in the soft tissue of the turbinate and is activated and while applying the thermal energy at or around the tip of the electrode. This technique heats the tissues to temperatures of 400–600 ° C and can cause significant surrounding tissue injury and thermal damage of the overlying mucosa [8].

Fradis et al. found a 76% improvement of nasal breathing in patients treated with submucosal electrocautery 2 months after surgery [9]. However, Jones and Lancer

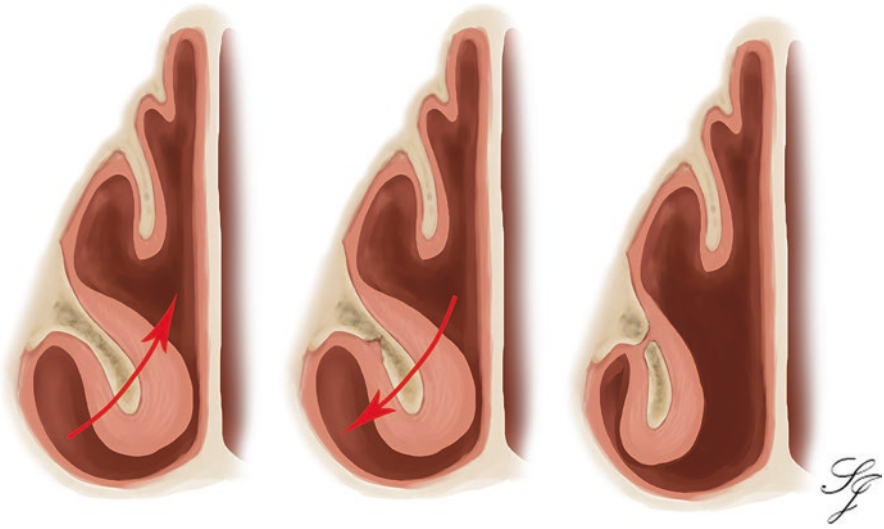

Fig. 31.4 Infracture and outfracture of the inferior turbinate (avoid greenstick fracture) (Courtesy of TESAV)

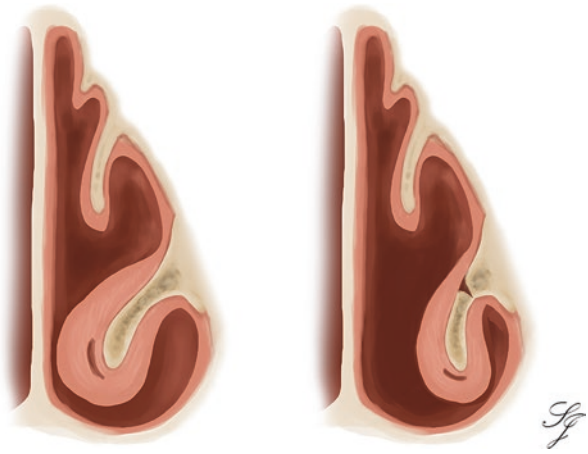

Fig. 31.5 Legler operation. If this angle is 90°, then the bony attachment should be cut or fractured from the lateral nasal wall with osteotomes or chisels (Courtesy of TESAV)

reported that the improvement is not permanent and there was no significant difference between the nasal resistances before and 15 months after surgery [10]. Therefore, electro-cautery of the IT is rarely performed today.

31.2.1.3 Submucosal Radiofrequency Coblation

Radiofrequency tissue reduction of the IT is another common method to reduce the soft tissue hypertrophy. This technique uses high-frequency sound waves. This technique heats the tissues to temperatures between 60 and 90 °C to induce submucosal tissue destruction and fibrosis. Therefore, heating is significantly less than submucosal cautery. Radiofrequency ablation (RFA) is an effective, easy, and safe

mucosa-preserving surgical technique [11]. Harsten demonstrated 82% improvement in patients on short-term follow-up (4–9 months), whereas the long-term improvement was only 78% (21–30 months) [12]. This procedure has a major advantage in that it can be easily performed under local anesthesia in the clinic setting or in the OR during sinus or nasal surgery.

31.2.1.4 Powered Submucosal Turbinate Reduction

The powered instruments can reduce the submucosal soft tissue while preserving the epithelium. The head of the IT is entered through a small incision, and the flap is dissected all the way back to the tail of the inferior turbinate using an elevator and a submucosal pocket is formed. A small 2.0–2.9 mm microdebrider blade is inserted through a pocket and advanced with the cutting surface facing laterally [7]. The flap should not be perforated. In the posterior part of the turbinate, there may be bleeding from the posterior lateral nasal and sphenopalatine arteries due to injury to vessels [13].

A 2015 meta-analysis comparing radiofrequency ablation with microdebrider inferior turbinate reduction found that both techniques were effective in improving visual analog scale-rated nasal obstruction and acoustic rhinomanometry results, but the median follow-up was only 6 months. They demonstrated no significant differences in outcomes based on technique [14]. However, it is not common for the powered IT procedure to be performed in the clinic setting, which can be a disadvantage.

31.2.1.5 Submucosal Inferior Turbinate Bone Resection

If the turbinate bone is hypertrophic or enlarged, it may be resected. A mucoperiosteal flap is elevated medially off the underlying turbinate bone using a Cottle or Freer. A submucosal tunnel is created, and the bone is resected. A portion of the bone can also be resected using the submucosal powered microdebrider technique.

Turbinoplasty and SMR involve the remodeling of the IT with the removal of submucosal tissue with or without bone removal. This is performed without the removal of the external mucosal layer to reduce the chances of synechiae formation or loss of receptors located on the turbinate's mucosal surface [15].

Greywoode et al. described the use of an ultrasonic bone aspirator to remove the inferior turbinate bone. This device uses ultrasonic waves to emulsify bone, with concurrent irrigation and microsuction of bone particles producing a clean surgical field; this reportedly enables the removal of the inferior turbinate bone without thermal or mechanical injury to the surrounding soft tissue or mucosa [16].

31.2.1.6 Turbinoplasty

After an incision at the anterior edge of the IT, the mucosa on the medial surface of the IT is subperiosteally elevated. The inferior half of the bony IT is cut with the mucosa on the lateral surface of the IT. The elevated mucosa on the medial surface is then returned laterally, and the bony surface is covered with the mucosa, and no bony surface is left open. The inferior meatus is packed, and the mucosal flap is kept in place (Fig. 31.6) [3].

31.2.2 Mucosa Sacrificing Techniques

The nasal mucosa is an organ responsible for mucociliary clearance and immune defense and therefore should be preserved as much as possible. Although not preferred, some mucosal sacrificing techniques have also been reported in the literature.

31.2.2.1 Partial Turbinectomy

The IT can be partially resected with concha scissors. This partial resection can include either the inferior part, or the posterior part, or the tail of the IT. If the posterior part or the tail of the IT is polypoid, it can be safely removed by using a snare. Acute or delayed bleeding is a major complication.

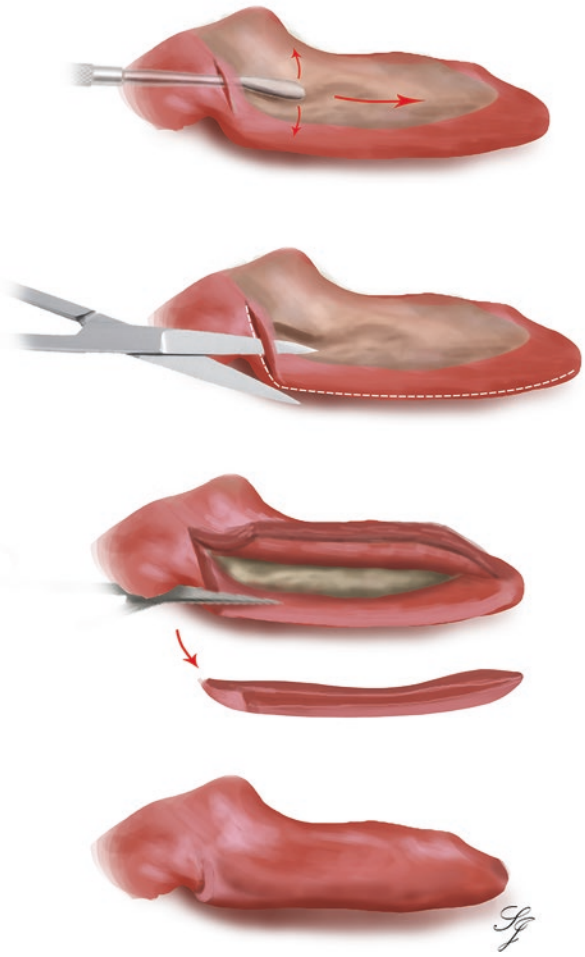

Fig. 31.6 Turbinoplasty (Courtesy of TESAV)

31.2.2.2 Laser

Lasers can be used for soft tissue hypertrophy. A number of lasers have been used for this technique, including the argon laser, the carbon dioxide (CO2) laser, the diode laser, the holmium-yttrium aluminum garnet laser, the potassium titanyl phosphate (KTP) laser, and the neodymium-yttrium aluminum garnet (Nd:YAG) laser [17]. Lasers work well on soft tissue and also provide immediate coagulation of any bleeding sites.

31.2.2.3 Argon Plasma Coagulation

An ionized argon gas current creates 1–2 mm contact-free thermocoagulation in the tissue between the handpiece and the tissue. The handpiece is applied slowly over the entire length of the lower one-third to one-half of the inferior turbinate in 3–4 parallel lines. Direct contact of the applicator tip with the turbinate tissue is avoided because it prevents the desired effects [18].

31.2.2.4 Total Resection

Total or "radical" turbinectomy is the complete resection of the inferior turbinate by detaching it directly at its site of the lateral nasal wall attachment. This technique can reduce the nasal resistance by up to 50% [19]. Total resection may cause excessive mucosal drying, scarring, foul-smelling nasal discharge, and recurrent epistaxis and severe long-term complications such as atrophic rhinitis and ozena (i.e., empty nose syndrome) secondary to the loss of the inferior turbinate in which the patient has an objectively patent nasal airway but has a sensation of obstruction [20].

31.3 Conclusion

As mentioned above, there are different surgical techniques for inferior turbinate hypertrophy. All techniques are somewhat effective at improving nasal obstruction due to turbinate hypertrophy not responsive to medical therapy. A randomized clinical trial compared the following six techniques: turbinectomy, laser cautery, electrocautery, cryotherapy, submucosal resection, and submucosal resection with lateralization. Significant improvement was noted initially in all groups ($p < 0.001$); however, the duration of improvement varied. Patients with electro-cautery or cryotherapy had progressive worsening of nasal resistance, and the patients who underwent laser cautery had reduced nasal volumes over the 6-year follow-up. Only the patients with submucosal resection achieved normal parameters for mucociliary transport time and secretory IgA concentration. The submucosal resection patients also experienced better quality of life scores and, when combined with outfracture, had the best results [20].

The selection of the surgical technique depends on the anatomy of the inferior turbinate (whether the hypertrophy is more related to bone or mucosa), the extent of the hypertrophy (whether it is more anterior or posterior), the response to previous interventions, available equipment, cost, desire for general anesthesia, and the surgeon's skill [21]. Mucosal sparing or conservative techniques should be preferred if possible. However, the technique to select for IT surgery should be individualized to the clinical situation.

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The Role of Allergic Rhinitis for Professional Voice Users

32

Necati Enver and Michael J. Pitman

32.1 Professional Voice Users

Titze et al. describe professional voice users as individuals whose livelihoods depend partially or entirely on their voice [1]. They include not only performers such as singers and actors but also professionals such as teachers, salespeople, managers, call center operators, attorneys, and doctors [1]. Professional voice users comprise 25–35% of the US working population, and their voice problems may interfere with job performance and impact costs for both employers and employees [2].

Voice users can be grouped into four categories according to their dependence on their voice [3]: **Elite vocal performers (Level 1)** always require maximum vocal performance and need superior voice quality, pitch, range, and volume; most professional singers and actors are part of this group. For **professional voice users (Level 2),** the voice is an essential part of their work life. They mainly need vocal endurance and stamina over prolonged periods, and voice quality is a secondary concern for them; teachers, lecturers, customer service workers, and fitness instructors are in this group. **Nonvocal professional voice users (Level 3)** would be able to perform their job with mild dysphonia, but they would be unable to fulfill their professional commitments if they had moderate or severe dysphonia; even if they could accomplish their work-related tasks, they would lack the vocal quality needed

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_32

for their professional image. Lawyers, doctors, and managers are the main members of this group. **Nonvocal nonprofessional voice users (Level 4)** are the remaining individuals, who do not rely on their voice for their occupation. In this chapter, "professional voice user" refers to Levels 1–2 [3].

Voice disorders have a negative impact on society. A study investigating the economic impact of vocal attrition for public school teachers in Miami-Dade County revealed that the yearly hoarseness-related cost for 961 responders was approximately $12 million in absenteeism- and presenteeism-related costs [4]. There is also a significant psychological impact on patients. Salturk et al. found that both voice professionals and nonprofessional voice users with vocal dysfunction experience abnormal levels of anxiety and depression with professional voice users being significantly worse [5]. Other studies have similarly found stress, anxiety, and depression to be common among patients with glottal insufficiency, muscle tension dysphonia, and vocal fold lesions [6, 7].

32.2 Direct Effect of Seasonal Allergies on the Larynx

Research has repeatedly demonstrated the association between allergies and vocal impairment. Individuals with allergic rhinitis have been found to have greater prevalence of dysphonia than nonallergic individuals [8, 9]. Additionally, vocal performers with laryngeal symptoms are 15–25% more likely to have allergic rhinitis than those without vocal symptoms [10]. Allergy-related vocal symptoms are typically attributed to the secondary effects of allergic rhinitis, postnasal drip, asthma, or medications used to treat upper and lower airway allergies. However, recent studies exploring the direct and indirect effect of allergens describe a more complicated picture.

Recent animal and clinical studies demonstrate the direct inflammatory effect of allergens on the larynx. In a prospective, double-blind, placebo-controlled crossover study, five healthy patients with no reactive airway in a methacholine challenge test were given inhalants transorally. All patients presented with an increase in the phonatory pressure threshold, increased subglottic pressure, and indirect signs of increased mucosal inflammation when compared to placebo inhalation [11]. A recent animal study with Indian pigs exposed to a combination of iron soot with the house dust mite allergen for 6 weeks demonstrated increased submucosal and epithelial eosinophilia in the pigs' glottis, subglottis, and trachea [12].

Observational studies show that airway allergic inflammation in response to an allergen is not confined to one specific organ. Rather, similar responses are triggered along the respiratory tract [13]. These responses are due to local inflammatory processes as well as a systemic response produced by the migration of pro-inflammatory mediators through the circulatory system. An antigen's stimulation of one respiratory site can result in the expression of inflammatory cytokines at a location distant from the site of stimulation. This is a phenomenon

known as inflammatory crosstalk [14]. In allergic rhinitis, activation of local lymphocytes in the nose affects the activation of immune cells in the bone marrow. Inflammatory cells migrate from the bone marrow to the respiratory system and cause inflammation in parts of the respiratory system that have not encountered the allergen. These findings suggest the upper and lower airways should be viewed as a single functional unit. This concept is known as the unified airway. It includes the nose, paranasal sinuses, pharynx, larynx, trachea, bronchi, and pulmonary alveoli [15].

32.3 Evaluation of Professional Voice Users for their Allergy-Related Symptoms

A comprehensive history and physical is a crucial part of any medical visit. There are elements of the history and physical related to allergy that are of particular importance to professional voice users compared to the typical patient. This section will focus on these issues.

32.3.1 History

The classic symptoms of seasonal allergic rhinitis are recurrent episodes of sneezing, pruritus, rhinorrhea, nasal congestion, and lacrimation that occur after exposure to the offending allergen.

The literature demonstrates that patients with rhinitis (allergic rhinitis or nonallergic rhinitis) have a higher prevalence of dysphonia and decreased voice-related quality of life, as well as more severe chronic laryngeal symptoms [16]. Allergic respiratory disease can affect vocalization in many ways depending on the affected organs [13].

Healthy voice production involves three main factors: resonance, supple vocal fold vibration, and pulmonary airflow. If any of these systems are affected by allergy, it can result in dysphonia.

32.3.2 Sinonasal Symptoms

The nasal cavity and paranasal sinuses play an important role in forming the voice's resonant characteristics. These structures amplify selected harmonics of the sound produced by the vocal folds. Any pathology that affects the sinonasal cavity can affect which harmonics are amplified and how resonance is perceived. Allergic rhinitis or infective rhinitis or sinusitis or nasal polyps, for example, can all result in edema of the nasal cavity and sinuses with resonant changes. For professional voice users, even minor changes in the sinonasal airway can cause a change in their vocal production and impact their stage performance and stamina.

32.3.3 Laryngeal Symptoms

One of the main complaints among patients who are professional voice users is postnasal drainage from increased nasal secretions. This not only is irritating but also transmits inflammatory mediators to the larynx and pharynx stimulating local reaction, irrespective of their effect on the sinonasal cavity [14]. Patients with allergies frequently have thick laryngeal secretions and laryngeal edema or erythema [13, 17]. This all results in coughing and throat clearing which introduces mechanical trauma that further inflames the larynx and vocal folds. This inflammation of the vocal fold mucosa increases the mass of the vocal folds and changes their rheology [13]. This results in heavier or stiffer vocal folds that require more subglottic pressure to vibrate and hence more trauma from increased sheering forces applied to already inflamed and more vulnerable tissues. This cycle results in a downward spiral of imparting more trauma resulting in more inflammation. This presents as progressive symptoms of a deepening voice, decreased range of pitch, fatiguability, raspiness, and increased effort to speak and sing.

32.3.4 Pulmonary Symptoms

Patients with allergic rhinitis may also have reactive airway disease. The literature demonstrates a strong relationship between the severity of asthma symptoms and the presence of allergic rhinitis [18, 19]. *The pulmonary system is the power source of the voice as it imparts the subglottic pressure on the vocal folds that causes them to vibrate.* Patients with asthma experience reduced vital capacity and pulmonary airflow, impairing the phonatory power source. These changes result in decreased loudness of voice and changes in the range of vocal pitch, particularly for in the higher range. Patients also experience shortness of breath during phonation, which can be demonstrated by reduced maximum phonation time [20]. They may also have complaints of easy fatiguability and increased need to warm up for their performances [13].

These changes due to allergens impacting in the sinonasal cavity, larynx, and pulmonary system make a performer's vocal function unpredictable which is critical in the world of vocal performance. In addition, these circumstances increase the likelihood of acute and chronic vocal injury. During the patient encounter, the physician should be aware of the effect of allergens on vocal production and inquire about any vocal limitations. If these are conveyed by the patient, it is important to know of their duration, whether they are seasonal or perennial, what medications are used to treat the symptoms, and if there are any impending engagements such as rehearsals, auditions, or performances. This may affect the urgency and aggressiveness of treatment as well as possibly initiate a referral to a laryngologist for a more detailed evaluation of vocal function.

32.4 Examination

A professional voice user with allergic rhinitis requires a comprehensive ear, nose, and throat examination, including laryngeal examination. (Aspects of the comprehensive physical examination not pertinent to this chapter are discussed in other chapters of this textbook.) Laryngeal examination can be performed endoscopically using continuous light such as a halogen lamp. For patients with voice changes or who are professional voice users, a crucial part of the examination is videolaryngostroboscopy (VLS). VLS is an advanced laryngeal imaging tool that uses a synchronized flashing light passing through a laryngoscope in order to visualize vocal fold vibration in pseudo-slow motion that is not visible using continuous light. VLS allows the practitioner to identify perturbations in vibration that may be responsible for changes in the voice that would be missed if continuous light alone was used. This tool has become routine in clinical care by laryngologists. It is essential to making the appropriate diagnosis in 68% of patients and even alters diagnosis and treatment in 15% of patients [21, 22].

Visualization with a fiber-optic endoscope in the office provides the best means to fully evaluate the pharynx and larynx. Although not necessarily specific to the allergic larynx, there will often be findings of thick, tenacious mucus in the glottis, erythema, or paleness in the arytenoid mucosa and cobblestoning on the posterior pharyngeal wall (Fig. 32.1). In more severe cases, vocal fold edema can be seen which may impact mucosal wave and amplitude on VLS [23].

Professional voice users with allergies who continue performing during their exacerbations of allergic rhinitis have higher rates of injury and vocal fold lesions. The injuries seen in this patient group include vocal fold hemorrhages, polyps

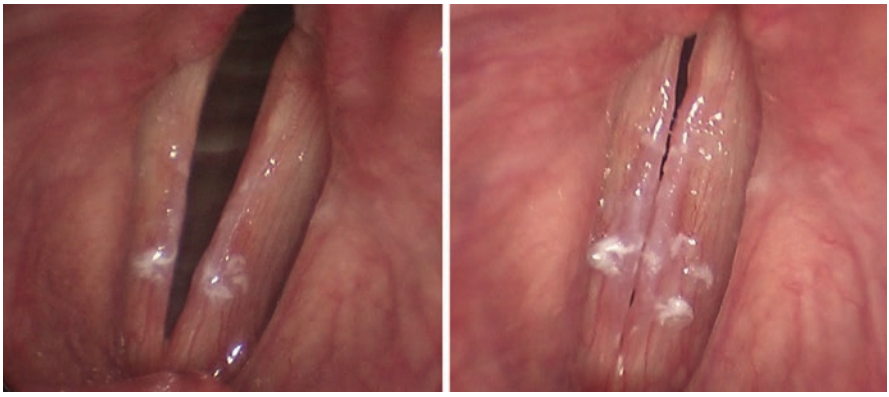

Fig. 32.1 Videolaryngostroboscopy examination of a patient with allergic laryngitis, which shows thick mucus in the glottis with increased erythema in the marginal edges of the vocal folds

nodules, and scars. In addition, the development of poor compensatory behaviors to overcome vocal dysfunction due to allergy may lead to laryngeal hyperfunction and muscle tension dysphonia [24].

32.5 Treatment

Allergic rhinitis is a chronic disease that negatively affects quality of life and productivity. Treatment should be based on the patient's lifestyle, work life, and severity of symptoms. Like every patient, professional voice users benefit from personalized treatment plans. Therapeutic management of allergic rhinitis consists of three major categories: avoidance, medical management, and immunotherapy. While the treatment algorithm for allergic rhinitis is discussed in the other chapters, this chapter will focus on the management modifications necessary when treating professional voice users.

32.5.1 Avoidance

Avoidance of the offending allergens is a noninvasive and theoretically effective treatment for allergic rhinitis [25]. Most of the strategies advocated for in the literature focus on indoor allergens, mainly dust mites [26]. However, professional voice users are exposed to different environmental factors than other groups. For example, politicians, teachers, lecturers, and presenters may work in crowded, sometimes dusty environments and thus experience more flare-ups than the typical office worker. During plays and musical performances, indoor environments could contain allergic irritants such as dust or mold in the theater, stage sets, studios, plastic masks, and old costumes. Some plays or concerts may be performed in open-air environments such as parks or stadia, increasing exposure to outdoor irritants such as grass, pollen, and fungal allergens.

These factors can increase the likelihood of voice-related allergic symptoms before, during, or after a vocal performance or vocally demanding work. Physicians providing consultation to these individuals should understand patients' voice demands as well as their unique environmental exposures.

32.5.2 Medical Treatment

Medical management is not entirely different for professional voice users compared to other populations. However, patient needs as well as current vocal demand and level of vocal function may affect the treatment plan. The side effects of treatment and how they specifically affect vocal function should be considered.

32.5.3 Antihistamines

Antihistamines are commonly used as an initial treatment of allergic rhinitis. There are several medications in this group, which have varying degrees of anticholinergic and sedating side effects. These side effects are directly related to the lipophilic activity of the molecule. First-generation antihistamines like chlorpheniramine and diphenhydramine are associated with their sedative and anticholinergic activity and are not recommended, whereas second-generation antihistamines such as loratadine, fexofenadine, and cetirizine have fewer side effects [27].

The anticholinergic activity of antihistamines is important for professional voice users, especially for performers. The primary concern is the drying of the vocal folds. Some forms of these medications are combined with decongesting substances such as phenylephrine, pseudoephedrine, or naphazoline, which help decrease nasal congestion and postnasal drip but increase dryness of the vocal folds as well.

Dehydration's negative impact on regular phonatory function is well-known [28–30]. Systemic hydration and superficial hydration are both crucial to have normal functioning vocal folds, particularly for people working in voice-demanding professions [31–33]. Patients who are performing and dehydrated are prone to experiencing vocal injuries [34]. Due to this, when possible, antihistamines are avoided in these patients. If they must be taken, patients should be aware of these side effects and should increase their hydration for the duration of the drug's administration. When necessary, topical hydration of the vocal folds should be supported with the inhalation of humidfied air, direct nebulization, and/or avoidance of drying environments [35].

32.5.4 Leukotriene Inhibitors

Leukotrienes are important molecules in the pathophysiology of allergic rhinitis. The most commonly used leukotriene inhibitor is montelukast sodium. Several clinical trials have demonstrated that montelukast is more effective than a placebo, and montelukast is as effective as antihistamines in controlling ocular and nasal symptoms of allergic rhinitis [27, 36]. Although montelukast decreases excessive mucus secretion, no vocal fold dryness has been reported, and montelukast can be used safely, even by elite vocal performers.

32.5.5 Nasal Steroids

Nasal steroids are one of the most effective drugs for the nasal symptoms of allergic rhinitis. Their effect begins within the first day, although it takes approximately 2 weeks to achieve the full benefit. Nasal steroids are beneficial for professional voice users with allergic rhinitis. They can be used as prophylaxis, preventing nasal

symptoms by starting them 1 week before predistinct allergy seasons such as pollen, tree, or grass seasons. They can also be used chronically or intermittently for perennial allergies. In themselves, nasal steroids do not have a deleterious effect on the voice. If successful, they may also decrease the need for oral medicines and their attendant side effects [27, 37].

32.5.6 Nasal Antihistamines and Ipratropium

In patients who do not achieve sufficient benefit from nasal steroids and leukotriene inhibitors, nasal antihistamine sprays can be added successfully. Similarly, ipratropium nasal spray is an excellent treatment for vasomotor rhinitis and thin watery rhinorrhea. Both medications can have some drying effects, but they do not appear to be as significant as those with oral antihistamines. Patients should be made aware these nasal sprays have the possibility of causing mucosal and vocal fold drying.

32.5.7 Oral Corticosteroids

In clinical practice, corticosteroids are widely used by otolaryngologists for phonotrauma and laryngeal inflammation. A short-term high dose of oral steroids may help reduce the inflammation on vocal fold folds. This change alone does not have the effect of curing the disease; however, it can be helpful to control the symptoms. In a recent experimental study, it has been shown that the anti-inflammatory cytokine IL-10 showed a 6.3-fold increase in the steroid treatment group versus the controls [38].

However, clinical experience shows decreased symptoms of laryngeal inflammation, the data showing anti-inflammatory change is limited in the literature [39]. In the recent Clinical Practice Guideline for hoarseness, one of the recommendations was against prescribing corticosteroids for patients with dysphonia prior to visualization of the larynx to avoid patients performing on steroids at higher risk to injury when they should otherwise be on voice rest [40]. In professional voice users, oral corticosteroids might be used after videolaryngostroboscopy in circumstances when urgent symptom control and return to performance are necessary and only vocal fold inflammation is seen without another attendant injury such as a hemorrhage or vocal fold tear. Although significant side effects of steroids are rare, they do occur, and the patient and physician should discuss them when considering their usage.

32.5.8 Immunotherapy

Allergy testing is helpful to identify which allergens patients should avoid. In addition, if specific allergies are identified, targeted immunotherapy is an option. Recently, immunotherapeutic treatment has moved forward with new developments including novel routes of delivery, modified allergens, allergen derivatives,

and combination therapy with biologics [41, 42]. These are also true for allergic rhinitis immunotherapy. It still takes several months to achieve significant results with the current treatment modalities. Modification of the immunological response toward the allergen can be achieved in a few years, but in some cases, injections or sublingual tablets need to be continued indefinitely. Immunotherapy should be considered for patients with severe allergies who are not well controlled with the above medications, for patients who experience side effects, or for patients who do not want to continue with chronic medical therapy. Due to the impact of allergies and allergy medication on the voice, physicians should be more aggressive in instituting immunotherapy in professional voice users.

Traditionally, immunotherapy is administered via subcutaneous injection. It is now available via the sublingual route (SLIT). Both treatment modalities were found to be of similar efficacy for allergic rhinitis and asthma [43]. For performers who are traveling extensively, SLIT may be a better alternative as keeping regular doctor appointments for injection could be difficult.

32.6 Conclusion

Allergic rhinitis may disproportionately impact a professional voice user who relies on their voice quality, stamina, and reliability. Symptoms are due to both the direct effects of allergen on larynx and indirect effects on the upper and lower airway. The most common findings are nonspecific increased and thickened laryngeal mucus and vocal fold inflammation. A complete head and neck history and physical examination are necessary to accurately diagnose the problem. Physicians treating professional voice users should be aware of the impact of allergies on vocal function, and they should consider the patient's unique needs when selecting a treatment option.

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Ideal Anaesthesia in Nasal Surgery

33

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33.1 Introduction

ENT surgery presents particular challenges to anaesthetists because of the need for both the surgeon and the anaesthetist to have access to the patient's airway. It is absolutely vital that the airway be secured during anaesthetic induction, but the surgical operations then performed on the airway may threaten this airway, which is a matter of concern to the anaesthetist. When the patient is being extubated, keeping the airway patent may be difficult because of oedematous passages, the placement of tampons and blockage or irritation of the airway resulting from bleeding. Thus, the end phase of anaesthesia in ENT operations is different from the usual pattern and safe anaesthetic practice in such cases calls for both knowledge and experience.

Nasal surgery forms a key component of ENT surgical practice. The nose and its adjacent structures may be operated on for a variety of purposes: aesthetic, functional, with cure in mind, or for palliation of symptoms. The nose plays a key role in keeping the airway open. The nasal portion of the airway joins first the pharynx and then the passage passing through the larynx and trachea before splitting into two sides to enter the lungs. The pharynx consists of both the oro- and nasopharynx. During operations on the nose, the nasal passage is anticipated to become at least partially obstructed, a situation which persists for some time post-surgically. It may be problematic to ventilate such individuals with a face mask when the nasal airway is blocked. A further issue is that nasal operations result in blood passing down the nasopharynx into the larynx. It is common to see that a patient is agitated following nasal procedures.

This chapter covers anaesthetic techniques used in patients having operations on the nose, including the entire period from before to after surgery and discusses the best methods to employ. Whilst there are three anaesthetic options in nasal surgery,

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_33

i.e. local, sedation or general anaesthesia, the ideal techniques need to be both inexpensive and non-invasive whilst providing the optimal comfort for patients and ENT surgeons to carry out their work [1, 2].

33.2 Preoperative Evaluation and Preparation of the Patient

Apart from occasional exceptions, the anaesthetic workup for candidates for nasal surgery differs little from other candidates for surgery. The anaesthetist's choice of technique principally depends on the aim of surgery and the approach to be used. There needs to be high-quality communication between the anaesthetist and surgeon to allow a discussion about the method to use, bearing in mind the patient's clinical characteristics and the operation being undertaken. The patient should be questioned about medical history and drug history, and systemic review should be undertaken [3]. If there is any acquired or congenital tendency to abnormal bleeding, this should be discovered and managed.

For any adult patient about to undergo planned surgery, asking carefully about and screening for obstructive sleep apnoea (OSA) should always occur, to identify any potential cases and to manage the anaesthetic risk through suitable steps before, during and after surgery [4]. OSA is a disorder of major clinical significance in the USA [5], being found in between 2% and 45% of the population. OSA without treatment raises the risk of circulatory disorders, such as hypertension and cardiac failure. Research has shown that patients at high risk of OSA also suffer a higher rate of complications in surgery [6].

The American Society of Anesthesiologists Physical Status (ASA-PS) (Table 33.1) scores correlate with increased morbidity and risk of death at the time of surgery. The ASA-PS category fits well with how complicated a patient's comorbidities are, the complexity of their drug history and the risk of various disorders. This scale can be used in assessing risk, being especially employed to gauge the chance of a poorer outcome post-surgery and the risk the patient will remain in the hospital or be readmitted later [7].

Prior to surgery, medication may be supplied to ease fear and anxiety and lessen excessive secretions and pain. The agents generally chosen are benzodiazepines, antihistamines and proton pump inhibitors. Patients must be told not to swallow any solid or liquid food within a minimum of 6 h prior to their operation [8].

For cases scheduled for nasal polypectomy, check in detail for possible evidence of allergy. Although the precise pathogenesis of nasal polyposis is unknown, many factors are probably involved. There is an association between nasal polyposis and asthma, cystic fibrosis, primary ciliary dyskinesia and aspirin hyperreactivity. It is thought that the condition affects 0.2–4% of the general population, but its frequency is much higher in asthmatic patients—up to 15%. In addition, nasal polyposis predicts asthma in approaching 45% of cases [9].

Post-surgical nausea and vomiting may arise due to secretions and blood gathering in the hypopharynx during nasal operations. Patients' risk of vomiting or feeling

Table 33.1 ASA PS (American Society of Anesthesiologist Physical Status Classification)

ASA PS classification	Definition	Examples
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to) current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; one or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	A declared brain-dead patient whose organs are being removed for donor purposes
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Abbreviations: *BMI* body mass index, *DM* diabetes mellitus, *HTN* hypertension, *COPD* chronic obstructive pulmonary disease, *ESRD* end-stage renal disease, *PCA* post-conceptual age, *CVA* cerebrovascular accident, *TIA* transient ischemic attack, *CAD* coronary artery disease, *ARD* acute renal disease, *DIC* disseminated intravascular coagulation

nauseous post-surgically (PONV: post-operative nausea and vomiting) should be evaluated. Risk factors include being female, a non-smoker, receiving opioids after surgery and having previously suffered from PONV or travel sickness. If patients are likely to have problems with PONV (high risks or low ability to tolerate), anti-emetic measures can be put in place [10].

In recent times, ERAS (enhanced recovery after surgery) has begun to take the place of conventional post-operative care. ERAS consists of patient education prior to surgery, employing anaesthetic techniques appropriately, particularly the use of analgesics, correct surgical strategy, and concentrated postoperative rehabilitative treatment [11].

33.3 Anaesthetic Methods

33.3.1 Local Anaesthesia

For certain patients undergoing sinonasal procedures, the infiltration of local anaesthetic is a reasonable choice. This has the benefit that surgical analgesia can be provided without the need to insert an airway or use positive pressure ventilation. Some authorities propose that endoscopic sinus surgery (ESS) is safer under local anaesthesia, since the patient retains awareness and can warn if the eye socket is inadvertently entered, as they will report pain [12].

Using local anaesthesia alone, septoplasty is also possible, a technique that offers significant benefit in fast-track surgery. With this technique, the operating surgeon assumes the central role in all the patient's care. The initial key step is diagnosing correctly and identifying suitable surgical candidates [13]. When local anaesthesia is delivered at the right level for the patient and procedure, the period spent performing surgery may in some instances be shortened [12].

33.3.2 Sedoanalgesia

In sedoanalgesia (SDA), sedation is not so marked as to prevent spontaneous breathing, and the patient can still co-operate with the procedure. The most frequently employed agents are opioids plus benzodiazepines. Some other anaesthetic medications are also suitable if the doses are appropriately reduced: thiopental, ketamine, propofol, and dexmedetomidine. It is important to remember that the security of the airway is less certain as the number of agents and the dose increases.

Sedoanalgesia has the advantages that operations may be quicker, there is less loss of blood, and anaesthetic equipment is not required. The drawbacks, as compared to general anaesthesia, are less able to secure the airway in an emergency, the likelihood of patients' aspirating, and the need for a co-operative patient [14]. The hazard presented by aspiration is the main reason that anaesthetists tend to prefer the use of a general anaesthetic for operations on the sinus and nose. Skilful haemostatic management does, however, lessen the chance of aspiration. It is essential for sinonasal surgery using SDA that the patient obeys commands, and the anaesthetist can monitor this closely. Whilst it is an advantage to be able to ask the patient to do particular things during the operation, unexpected movement by an awake patient may add to the difficulties for the surgeon [1].

33.3.3 General Anaesthesia

The majority of nasal operations involve a general anaesthetic (GA). GA affords the greatest control over the airway, helps ensure haemodynamic stability, and permits surgery on deeper structures to be more readily performed. Since the patient's reflexes are absent, surgery is more easily carried out. The supraglottic airway

(laryngeal mask) is now used in place of endotracheal intubation in a number of operations. A laryngeal mask airway forms a cover over the opening of the larynx. It offers greater protection from blood and secretions to the upper airway than endotracheal intubation. Research has shown, however, that the supraglottic airway protects the lower airway less well than endotracheal intubation [15].

Anaesthetic induction may be achieved by intravenous injection and then maintained by inhalational agents or through total intravenous anaesthesia (TIVA—by definition, solely using intravenous hypnotics and analgesics for anaesthetic induction and maintenance). If a patient has previously suffered from malignant hyperthermia, TIVA is necessary, and it may also be advisable in individuals with a high risk of PONV. This anaesthetic method has become more widely employed thanks to the invention of target-controlled infusion (TCI) devices, which make it easier to move between the induction and maintenance phases of anaesthesia [16].

Guidelines are supportive of the idea that TIVA may be advantageous in terms of operating conditions and recovery post-surgery. TIVA may be especially suited to a number of different groups of patients, amongst which are those undergoing surgery on the nose [17]. A popular combination is remifentanil with propofol. It is worth considering that reports by patients of being awake during general anaesthesia have been more common with TIVA, although most such incidences could have been avoided [16]. It is advised that anaesthetists keep checking how deep anaesthesia is. Remifentanil has high selectivity for the m-opioid receptor, at which it has agonist activity. It begins and stops working rapidly, has effects on the cardiovascular system which can be controlled and is suitable for dose titration. Its usefulness in TIVA comes from its rapidity of onset, dose-responsive circulatory effects and analgesic action. Despite these advantages, however, there have been reports of the agent causing hypotension, excessive cardiac slowing and greater need for opioids post-surgically. Increasingly, studies have compared remifentanil with dexmedetomidine [16].

When patients receiving dexmedetomidine were compared with controls, it was observed that inflammatory cytokine titres were lower. Dexmedetomidine creates analgesia by an action on alpha-2-adrenoceptors located in the locus coeruleus and the spinal cord. The frequent side effects when using this agent are nausea and vomiting, sedation, low blood pressure and excessive cardiac slowing [18].

33.3.4 Controlled Hypotension

A number of different techniques to lessen blood loss during surgery have been evaluated. One non-pharmacological approach is to place the patient in a reverse Trendelenburg position. Pharmacological techniques tried are corticosteroid administration pre-surgically; adrenaline injection to mucosal surfaces prior to surgery; intravenous or topical tranexamic acid; and adrenaline applied topically several times intraoperatively with adrenaline-infused cottonoids [19]. When such agents are to be used surgically, the anaesthetist needs to be aware, since inhaled

anaesthetic agents can potentiate the ability of adrenaline to provoke abnormal cardiac rhythms.

It has been proposed that deliberate lowering of blood pressure during operations on the nose may lessen bleeding and make surgery easier. To achieve this, systemic vascular resistance (SVR) or cardiac output (CO) can be lowered one at a time or together. The mean arterial pressure is the product of SVR times CO.

SVR may be lowered by means of a vasodilator agent such as nitroprusside, but this can also increase blood loss by the same mechanism. It has been proven that esmolol (a beta-antagonist with a short duration of action) given during surgery is superior to sodium nitroprusside. The best conditions for surgery obtainable with esmolol are when the diastolic pressure is just under 65 mmHg, i.e. a modest decrease.

Infusing magnesium promotes hypotension through lessening both CO and SVR. Surgical conditions are improved using this agent, but the downside is longer-lasting anaesthesia, post-surgical sedation and potentiation of neuromuscular blockade [20]. Remifentanil, with a very brief action, also improves surgical conditions, which may be thanks to its effect on the cardiac rate, output and vascular tension. Indeed, remifentanil has equivalent efficacy to both nitroprusside and esmolol in the lowering of blood pressure.

It is also possible to produce a hypotensive state intraoperatively by the use of hypotensive drugs acting agonistically on alpha-2-adrenoceptors, e.g. dexmedetomidine or clonidine. Nonetheless, the anaesthetist should be aware that there is an approximately 0.6% risk of organ failure due to hypotensive ischaemia [19].

33.4 Post-surgical Care and Analgesia

Post-surgically, adequate pain control can usually be achieved by the use of local anaesthetics and the administration of paracetamol and COX-2 inhibitors before and during the procedure [21].

There is a growing trend to utilise peripheral nerve blockade. For patients having surgery on the nose, general anaesthesia coupled with the blockade of the infraorbital nerve on both sides of the face is adequate for pain relief after surgery and means fewer additional painkillers will be needed [22].

The sphenopalatine ganglion can be blockaded by transpalatal infiltration of the pterygopalatine fossa. This technique supplies anaesthesia to the posterior septum, middle turbinate, sphenoid sinus and posterior ethmoid cavity. Localised anaesthetic infiltration coupled with agent release from nasal packs gives pain relief after surgery. The degree of analgesia obtainable is linked to the concentration, dosage and choice of local anaesthetic [23].

Local anaesthetic agents possess varying effect durations. They may be grouped as short- or long-acting. Short-acting agents act for up to 4 h. Examples are procaine, chloroprocaine, tetracaine, lidocaine, mepivacaine, prilocaine and tramadol. Long-acting agents act for longer than 4 h. Examples include bupivacaine, levobupivacaine, and ropivacaine [23].

33.5 Conclusion

Anaesthetists caring for patients undergoing nasal operations aim for a relaxed patient with an airway clear of contamination, who will have little or no pain post-surgically, will have no nausea, and will soon be fit enough to be sent home from the hospital. To render surgery less liable to complications, there are methods available to lessen blood loss and give ideal conditions for surgical intervention.

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Are Antifungals Effective in Rhinosinusitis?

34

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34.1 Introduction

It is now more popular to refer to rhinosinusitis rather than sinusitis, since inflammation virtually never occurs in the sinuses alone, without a nasal component [1–3]. Nonetheless, the FDA, in its draft guidance for how drug development should proceed, stresses that, with the exception of antibiotics, agents targeting sinusitis must have separate effects on sinus and nasal inflammation [4]. In other words, drugs for sinusitis need to have a demonstrable specific effect on sinusitis and not simply on rhinitis. However, both laboratory-based and clinical methods to grade the severity of CRS have low reliability, sensitivity and specificity, and this leads to problems when attempting to assess the efficacy of particular therapies [5].

It is probable that expert disagreement on how to define CRS stems from the multifaceted nature of the disorder and from our imperfect knowledge about the underlying pathogenesis of sinus mucosal inflammation. It has been hypothesised that a number of different processes may drive inflammation: infection by bacteria (which may then produce a biofilm and secrete supertoxins), infection by viruses, allergic responses to fungal organisms (allergic fungal sinusitis), infection by fungi (invasive), immune malfunction targeting non-pathogenic fungal organisms found throughout the environment, humoral immunodeficiency and rhinitis of allergic and nonallergic type. This lack of clear diagnostic criteria to permit recruitment into trials, due to the disparate nature of CRS, coupled with, at best, a partial knowledge of

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_34

the disorder's pathogenetic basis, results in a situation where clinicians need to rely on a slender evidence base when deciding what therapy to offer patients [5].

Fungal spores are frequently discovered in the nasal cavity and are present in inspired air. Whilst it is not certain that fungi are involved in every type of CRS, there are data supporting a part for fungi in the development of CRS in a subgroup of sufferers. Antimicrobial therapy aims to destroy fungal spores or arrest their development and is delivered either topically (i.e. intranasally) or systemically (taken orally) [6].

CRS involves inflammation of both the nasal lining and the sinuses. Ever since the mycological connection was first proposed towards the end of the 1990s, controversy has raged over the use of antifungals in CRS. It has been clearly demonstrated that fungi stimulate the immune response in a subset of individuals with allergic fungal sinusitis (AFS), but this does not necessarily mean that fungi actually cause CRS or that antimicrobials targeting fungi will have a useful role in therapy for the condition [7].

Pathophysiological investigations aiming to uncover the basis of CRS allowed the insight that eosinophilic degranulation can occur when fungi are present [8]. Fungal organisms have been frequently isolated from the nasal secretions of CRS sufferers and healthy individuals alike [8]. Another study found that, in cases of CRS, an abnormal immune response orchestrated by Th2 cells was seen in circulating blood mononuclear leukocytes [9].

34.2 Antifungal Therapy for CRS

The precise relationship between fungi and CRS has been the subject of significant debate amongst researchers [10]. According to Ponikau et al. [11], colonising fungi may provide the trigger for a chronic inflammatory response in CRS, both CRS with and without polyposis. Fungal microbes were found 96% of the time in CRS sufferers. Notably, however, fungal microbes were found invariably (100%) in the healthy controls. Another finding was that interleukins 13 and 5, which mediate eosinophil activation, were secreted by immunocytes from individuals with CRS in response to fungi typically found in the air [12]. Researchers from the Mayo Clinic report that eosinophilic degranulation occurs in vitro when *Alternaria alternata* organisms are present [13]. The study authors reach the conclusion that particular free-living fungal organisms play a key role in worsening asthmatic and atopic inflammatory responses. The hypothesis that fungi are implicated in the inflammatory response found in CRS has led many to propose topical or systemic antimicrobial therapy be used to combat the disorder [13].

Some researchers have gone so far as to claim that most cases of CRS are linked to fungal infection of the sinuses [8]. Ponikau et al. are advocates of this view and support the use of topical antifungal agents in CRS [8]. Others have pointed out that colonisation by fungal organisms is highly prevalent in both those with CRS and those who are healthy [14]. The literature reflects the increasing debate surrounding

the issue, and there are supporters and opponents of the use of antimicrobial agents, both topical and systemic [15].

Whilst there is high-quality evidence indicating that fungi play a role in the immune response in CRS [16], it does not follow that antimicrobials will necessarily have efficacy in treatment. It is conceivable that the immune system is acting inappropriately and thus leading to CRS and that fungal organisms are merely bystanders, which then become targets of the immune response. The fact that fungi are so widespread in the environment and in the human sinus is notable [14].

Supporters of the use of antimicrobials in CRS and AFS point out that it is the presence of fungal organisms within the mucosa of the nose and sinuses that provokes an inflammatory response from a sensitised immune system, resulting in eosinophil-dominated inflammation. The rationale for treatment is therefore to destroy fungus and remove this trigger [8]. Topical antifungal agents have so far not shown clear benefit in CRS. A single trial (out of five such undertaken) produced an improvement in radiological and endoscopy scores, but this was not reflected in symptom reduction [17]. The outcome measures were highly different, which may reflect different characteristics of trial participants or because the disorder is so multiform. In one trial, the control group performed better on symptomatic scoring and quality-of-life improvements specifically related to the disorder [18–29]. When the results were aggregated for all the studies, the placebo group did better at the level of statistical significance.

34.2.1 Intranasal Antifungal Agents for CRS

The most up-to-date data are from a trial involving 64 patients with CRS without polyposis and employing randomisation, double-blinding and placebo control [19]. This is the first time antifungal agents have been used in patients with CRS without polyposis. The inclusion criteria were having nose-related symptoms for 12 weeks, mucosal oedema or pus-filled rhinorrhoea on rhinoscopic examination, and imaging consistent with a diagnosis of sinusitis. The main exclusion criterion was nasal polyposis. Amphotericin B solution was used to administer the drug. The amphotericin had to be kept in the refrigerator. Placebo was a liquid with the same yellow appearance. The dosage of amphotericin used was 20 mg/4 mL water o.d. for a duration of 4 weeks. The participants were forbidden to take other antimicrobials, oral antifungal drugs, steroids or histamine blockers by mouth. For outcome measures, this research utilised the Rhinosinusitis Outcome Measures-31 (CRSOM-31) and rhinoscopy (scored by the Lund system) at 2 and 4 weeks after joining the study. The authors do not report their power calculation in the statistical analysis. The group receiving the active agent had CRSOM-31 scores that were significantly lower at 2 weeks compared to the placebo group, but the difference was not maintained at 4 weeks. Endoscopic scoring was the same for both groups. Pretreatment lavage washings were cultured. Sixty-six percent of specimens produced positive mycological culture.

Post-trial specimens from the active treatment group grew fungal organisms in 55% of cases, implying that amphotericin B failed to eliminate viable fungi [19].

The biggest study of the role of amphotericin B used topically in the nasal cavity in CRS examined 116 cases of CRS (both with and without polyposis) and was in the form of a double-blind, placebo-controlled multicentre RCT [20]. To be included, participants had to be at least 18 years old, with signs and symptoms of CRS, with CRS confirmed by rhinoscopy (with or without polyp growth), a score above 5 on the Lund-Mackay scale for sinus CT, and to have had previous functional endoscopic sinus surgery. Cases of AFS were reported to have been excluded, although the authors do not state how the AFS diagnosis was operationalised. Nasal corticosteroids and antibiotics (as needed) were permitted, as were oral steroids for indications other than CRS. Amphotericin B was delivered at a dose of 10 mg daily, divided into b.d. doses dissolved in 25 mL sterile water with 2.5% glucose. The Emcur nasal douching device was employed. Solutions were prepared monthly, with placebo having identical appearance. The outcomes were assessed by using a symptomatic visual analogue scale and rhinoscopic assessment of the nasal mucosa. The RSOM-31 and SF-36 standardised questionnaire instruments were used. The study was powered to detect a 25% difference in scores between active agent and placebo. The completion rate for trial participants was 83%. In terms of outcome measures, the two groups were not significantly different. Whilst under 20% of participants did take antibiotic therapy or oral steroids during the trial, there was equal distribution of such individuals between the two groups [20].

Another study with randomisation, placebo control and double-blinding examined 24 individuals who received either amphotericin B intranasally or a similar-appearing inactive agent. The trial was a pilot study over 6 months [21]. The recipients of the active agent showed more reduction in mucosal width and had better scores on endoscopy than those receiving placebo. However, when the symptom scores (assessed using SNOT-20) were compared, the groups did not differ significantly. EDN (eosinophil-derived neurotoxin) levels were lower in those receiving amphotericin B, but no difference was observed in interleukin 5. Both groups had the same degree of colonisation with *Alternaria* organisms. The key message from this study was that amphotericin B results in radiological improvement (an objective outcome measure), EDN levels also fall, and the amphotericin solution is satisfactorily delivered to the sinus. However, caution needs to be exercised in drawing conclusions from the study due to no improvement in symptom score, no systematic assessment of medication concordance and the fact that the *Alternaria* organisms did not reduce in number through treatment [21].

A different trial of antifungals studied 78 individuals with CRS over a period of 8 weeks. The dose of 4.8 mg/day (eight sprays per day of 100 μL each with an amphotericin B concentration of 3 mg/mL) was given by an intranasal spray device [22]. This nasal delivery system was adopted to avoid confounding due to nasal lavage, which is potentially beneficial in its own right. The sample size was chosen to allow the detection of 50% difference in CT-based scores following treatment. This was the primary outcome, whilst quality of life and a rhinoscopic assessment were secondary outcomes. Mycological culture and the polymerase chain reaction

(PCR) were also carried out. The study detected no difference in imaging score, nor on quality of life, between the two groups. Moreover, the symptom score was worse in the group given active agent, a result that was statistically significant. A statistical analysis divided the participants into four subgroups (fungal elements before and after treatment, fungal elements before treatment only, fungal elements after treatment only, fungal elements not detected before or after treatment) to evaluate the effect of amphotericin B. Imaging score, quality of life and rhinoscopic evaluation revealed no significant differences [22].

Weschta et al. [23] performed a study to evaluate the effectiveness of nasally delivered amphotericin B in cases of CRS with nasal polyps. Treatment lasted 8 weeks. Symptoms were rated significantly worse in the group receiving amphotericin B.

Hashemian et al. [24] carried out research involving randomisation, double-blinding and placebo control with 54 individuals whose CRS did not resolve with conventional pharmacological therapy. Groups were assigned at random to be supplied either fluconazole intranasal drops 0.2% or inactive agent, alongside standard treatment lasting 8 weeks. The Sino-Nasal Outcome Test 20 (SNOT-20), endoscopic scores and radiological (CT) scores were used as the outcome measures. SNOT-20 ($p = 0.201$), endoscopic score ($p = 0.283$) and CT scores ($p = 0.212$) did not differ at the level of statistical significance between baseline and following the intervention, in either the group receiving amphotericin B or those on inactive placebo. As has been apparent in several other similar trials, the evidence does not support the use of topical antifungal treatment for patients with CRS.

34.2.2 High-Dose Oral Antifungal Therapy for Chronic Rhinosinusitis

One study, dating from 2005, examined the use of systemic antifungal pharmacotherapy in CRS in 53 individuals, all of whom were adults. The study was both placebo-controlled and double-blinded [25]. The agent chosen was terbinafine and treatment lasted 6 weeks. Participants were symptomatic and had evidence on CT of CRS. Alteration in the CT opacification score was taken as the principal outcome. The secondary outcomes were the clinicians' overall impression and the total score on the Rhinosinusitis Disability Index (RSDI). For each participant, mycological culture was performed, and a restricted number of samples taken from the nasal lining were assessed to quantify the concentration of terbinafine. There was no power calculation to guide the number of participants required. The groups did not differ in total opacification score, how successfully fungi were eradicated, RSDI or how the clinician rated the case overall. Whilst the research findings point to oral terbinafine not being a useful agent in CRS, caution needs to be exercised in drawing any conclusions, given that this was a pilot study only, and with several limitations [25].

Itraconazole by mouth has been employed adjunctively in treating allergic bronchopulmonary aspergillosis (ABPA). There are anecdotal accounts which suggest itraconazole may provide benefit in certain individuals with CRS with polyps. The

benefits demonstrated for itraconazole in ABPA are reducing dependence on corticosteroids, lowering IgE titres, whilst enhancing lung function, improving exercise tolerance and improving symptomatology. Antifungal antimicrobial therapy by mouth has been suggested as suitable for particular patients with allergic fungal sinusitis (AFS) [26–28], as well as non-allergic fungal sinusitis [27]. Both these disorders resemble ABPA in some respects. Anecdotal accounts also exist showing that individuals with Samter's triad (severe nasal polyp formation, asthma and sensitivity to aspirin) may also benefit from itraconazole [10].

34.3 The Dose of Therapy

Amphotericin B at a concentration of 100 microgram/ml in vitro was demonstrated to be unable to inhibit further growth of fungi, compared to a dosage of 200 or 300 μg/mL [24, 29].

Various concentrations of antimicrobial were used in different studies. This possibly affects how the drug works, given that fungi cannot grow if amphotericin B is present at a concentration of 200 or 300 μg/mL, but do continue growing if the concentration is only 100 μg/mL. In two of the studies, amphotericin B reached a level of 100 μg/mL [20, 30]. At present, there is debate about the ideal dose and about how the agent should be prepared, and this may affect clinical efficacy. There was no superiority of placebo over active agent when assessed radiologically. Whilst it is undoubtedly true that fungi are found everywhere in the environment and even in healthy sinuses, if CRS is present in certain forms, it may be easier to culture fungal organisms in samples from the sinus, and the disorder may affect how antifungal treatment actually works. In this scenario, then, fungi may be considered a cause, rather than just an innocent bystander, and antimicrobial therapy might then be indicated [7].

Currently, there is no good evidence for its use in CRS with or without nasal polyposis.

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How Does Nasal Polyp Formation Relate to Immunomodulatory Effects?

35

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35.1 Introduction

Chronic rhinosinusitis (CRS) is a common disease. The overall prevalence of symptom-based CRS in the population has been found to be between 5.5% and 28% [1]. CRS is divided into two phenotypes, CRS with (CRSwNP) and without nasal polyps (CRSsNP) [1]. Nasal polyps are benign mucosal swellings with varying histological patterns. The term "polyp" comes from the Greek "poly" (meaning "many") and "pous" (meaning "foot"), i.e. a lesion with many feet. The prevalence of CRSwNP is between 1% and 4% of the general population. CRSwNP does not show any particular ethnic predominance. The typical age of CRSwNP onset is middle adulthood. Peak age of incidence has shown to be 42 years [2].

Nasal polyps possess a peduncle, have a smooth surface and are jelly-like in consistency. They are the most frequently encountered intranasal mass in adults and are usually bilateral. The majority are benign. Indeed, a unilateral nasal polyp raises the suspicion of malignant neoplasia, nasal glioma, encephalocoele, angiofibroma, inverted papilloma, maxillary and ethmoidal malignant lesions or carcinoma of the nasopharynx. In a paediatric case of nasal polyposis, the clinician needs to be aware of the possibility of rare diseases such as cystic fibrosis and primary ciliary dyskinesia [3, 4].

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_35

CRSwNP is multifactorial in origin but invariably involves inflammation within the mucosa. The pathogenesis of the development of CRSwNP is probably related to aberrant host genome and environmental interactions in upper airway barriers [1]. CRSwNP is characterised by disrupted epithelium, mucosal oedema and abundance of inflammatory cells [5]. Although there are different endotypes of CRSwNP, the common pathological events in CRSwNP endotypes are characterised by innate immunity dysfunctions including aberrant mucociliary clearance, antimicrobial-, junction- and pattern recognition protein functions, activation of immune cells, mucosal leakiness, leukocyte infiltration and increased inflammatory mediators. Moreover, aberrant adaptive immunity responses, epithelial-to-mesenchymal transition, dysbiosis and abnormal microbiome-epithelial interactions may lead to aggravation and chronicity of the inflammation [5].

Nasal polyps usually develop in ethmoidal cells and protrude into the middle meatus, a functionally and anatomically important area of sinonasal drainage [1]. Mucosal inflammation, oedema and mucus of osteomeatal unit and middle meatus may lead to the aggravation of chronic inflammation and development of acute infective exacerbations. Infiltration of leukocytes, production of inflammatory mediators, epithelial disruption and dysfunction (such as by remodelling) all lead to oedema formation and aggravation of chronic inflammation.

CRSwNP diagnosis is based on clinical history and examination. The typical symptoms are nasal obstruction, poor or absent sense of smell and thick nasal discharges. Facial pain or pressure is less frequently reported symptom in CRSwNP patients, whilst it is more common in CRSsNP [6]. Physical examination needs to assess mimicking or coexisting conditions of CRSwNP. Proptosis or seeing double may signal inflammation spreading to the orbit from the sinuses or involvement of the central nervous system. Compared to anterior rhinoscopy, nasal endoscopy enables better views of the nasal cavity and thus is the golden standard in the diagnosis of CRSwNP. Sinus computed tomography (CT) scans are needed, even in paediatric patients, when complications are suspected or when surgery is considered/planned [1]. In addition, sinus (CT) scans are considered if symptoms continue despite adequate pharmacotherapy or if pathology is suspected to originate from or spreading to neighbouring organs (such as orbital-, cranial- or oral cavity) [7].

The histopathological diagnostics of CRSwNP is to rule out other pathologies and to assess the tissue eosinophilia, which has shown to be associated with the recurrence rate of CRSwNP [1]. Additional objective measurements include allergy testing, assessment of smell, assessment of microbiota and nasal functional tests and may be considered for special purposes [1]. Assessment of proteins from tissue, fluid, blood or urine samples are under research, and biomarkers may be in the future usable in therapy planning and following of severe CRSwNP.

35.2 Pathophysiology of Nasal Polyposis

Under normal host defence, Type 1, 2 and 3 profiles and their combinations eliminate viruses, helminths and bacteria/fungi, respectively [1]. In CRSwNP, environmental agents invoke pathological Type 1, 2 and 3 pathways, leading to chronic and

polyclonal responses against a large number of poorly characterised agents [1]. CRSwNP can be subdivided into endotypes, based on the predominance of Type 1, 2 or 3 cytokines. Asian CRSwNP patients tend to have lower expression levels of Type 2 cytokines than Western polyps [1]. Western polyps are characterised by Type 2 inflammation with a predominance of eosinophils, T-helper (Th) 2 cells and cytokines related to these cells, such as IL-4, IL-5, IL-13, eotaxin and eosinophil cationic protein [8–10]. Type 2 cytokines are responsible for the recruitment of mast cells, basophils and eosinophils involved in pathological immune responses. Novel pharmacological agents that can suppress the synthesis of these cytokines or inhibit their action have been and are currently developed and may provide advanced treatments for CRSwNP.

Eosinophilic CRS (eCRS) is a subtype of CRS. The definition of eCRS has been supported to be ≥10 eosinophils/high-power field, quantified by using 400x magnification of a microscope. (EPOS2020). The prevalence of eCRS in different populations and its risk-factors is currently under active investigation. At 11%, the polyp is defined as of eosinophilic allergic type. Using this figure as the cut-off value means 62.7% of nasal polyps are of the eosinophilic allergic subtype [10]. Nasal polyps are richer indicators of eosinophilic involvement (eosinophils themselves, eotaxin and eosinophil cationic protein) than healthy epithelium or other forms of chronic rhinosinusitis. eCRS has been shown to be associated with a greater degree of swelling and of greater severity [11].

Commensals likely play important roles in the development and homeostasis of healthy sinonasal mucosa [1]. Microbial imbalance (e.g. dysbiosis) and in particular the presence of *Staphylococcus aureus* (*S. aureus*) has been hypothesised to take part in the mechanisms of CRSwNP [1]. Also, other bacterial species and viruses may play some role and fungi in sporadic cases. Some evidence exists that the development or aggravation of CRSwNP is related to the formation of a sinonasal biofilm, which consists of the bacterial colony and extracellular matrix, resistant to the environment, host defence and treatment [1]. Many bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis and S. aureus* have been shown to form sinonasal biofilms. The proportion of people having sinonasal colonisation of *S. aureus* is 20–30%, and this prevalence is higher among eCRS and CRSwNP with asthma [1]. *Staphylococcus aureus* colonisation is usually associated with Type 2 cytokine profile via its enterotoxins. Type 2 inflammation might promote *S. aureus* colonisation. *Staphylococcus aureus* may also promote Type 2 inflammation by its capacity of secreting superantigenic toxins that have shown to directly trigger polyclonal IgE synthesis in polyp [1]. This response is different from that seen in allergy [12]. However, this initial adaptive response to the bacterial pathogenic attack may result in unmasking autoantigens on the basement membrane which can then stimulate an allergic autoimmune response [13]. A study showed that CRSwNP patients positive for IL-5 and specific IgE to *S. aureus* enterotoxins had a greater likelihood of being asthmatic [14]. Asthmatics have been shown to have six times higher risk of having specific IgE to *S. aureus* enterotoxins in their polyp tissue compared to polyp tissue of nonasthmatics [14, 15]. Staphylococcal superantigens seem thus to play a role in the aggravation of airway illnesses.

There have been several theories in the history explaining the variable pathology and development of nasal polyps. Polyps have in the past been proposed to represent a variety of different lesions: adenoma, fibroma, mucosal exudate, cyst formation within excretory ducts or oedema secondary to lymphatic or glandular constriction. Competing theories proposed that repeated infective episodes provoked lymphangitis or that glands became hyperplastic. Tos et al. [16] put forward a theory in which the epithelial continuity is disturbed and necrosis occurs, following which the lamina propria herniates and the epithelium is reconstituted. Newer molecular research has led to the suggestion that there are several endotypes of CRSwNP which can be differentiated from each other by the pattern of secreted cytokines. If true, this indicates that several pathogenetic mechanisms exist to explain polyp formation [17, 18].

Remodelling is defined as abnormal restitution of damaged tissues and its events, such as fibrosis, basement membrane thickening, goblet cell hyperplasia, epithelial barrier abnormalities osteitis and angiogenesis have been detected in CRS. The non-eosinophilic CRS (non-eCRS) has been characterised by a higher level of hyperplastic gland formation and heavy deposition of collagen [11]. Fibrosis and the laying down of collagen have been found in CRSsNP, despite eosinophilia, oedema is the predominant feature in CRSwNP [11]. Reduced numbers of glands and elongation of the existing canals and tubular glands have been detected in polyp tissue [19]. Overall, CRS has been characterised by increased glandular activity, hypersecretion of mucus and raised numbers of goblet cells [19, 20].

The normal turnover and repair of epithelial cells occurs via interplay with fibroblasts and is termed epithelial to mesenchymal transition (EMT) [1]. EMT has been detected in some CRS cases leading to acanthosis, acantholysis and a leaky barrier [1]. CRSwNP has also been characterised by diminished collagen and extracellular matrix degradation possibly via dysregulated metalloproteinases [1]. The study group performed Gene Expression Omnibus database search of polyp microarrays and detected that significant increase mRNA transcripts of collagen types X, VI and VIII and decorin messages (by Lumican) in nasal polyp tissue [21]. Matrix metalloproteinase (MMP) regulate the composition of tissues via degrading extracellular matrix components, such as collagen, elastin and fibronectin [22–24]. Single-nucleotide polymorphism of the MMP-9 gene may elevate the likelihood of developing CRS [22]. Degradatory action by MMPs might be crucial in the development of pseudocysts that have been detected in CRSwNP [19, 20].

Meng biopsied middle turbinate early-stage polyps (ESPs) with an intact stalk and pedicle and fully developed polyps (LSPs) from the ethmoid [25]. They detected more deficient epithelium in ESPs, whereas LSPs exhibited deficient junctional proteins, notably E-cadherin, zonula occludens-1 and occludin. ESPs possessed higher levels of TGF-β, stained more strongly for vimentin, and activated myofibroblasts were more prolific. These latter stained positively for α-smooth muscle actin (αSMA), a finding indicative of increased epithelial-to-mesenchymal transition (EMT), and showing attempts at repair were continuing. ESPs contained greater numbers of M2 macrophages, and fibronectin was more prominent, an indication of a widespread type 2 inflammatory reaction. ESPs had

a stalk with large amounts of collagen laid down, which reflects a more active role for fibroblasts in the first stages of polypogenesis [25].

Takabayashi et al. showed capillary leakage and thrombin activation by tissue factors whilst plasma fibrinogen is cleaved [26, 27]. The cross-linkages on the fibrin mesh were shown to be produced by factor XIIIA, which is secreted by M2 histiocytes. Because the epithelium of the polyp has lower expression of tissue plasminogen activator (tPA), the fibrin cannot be broken down [26, 27]. They also showed that increased polyp IL-13 would lead to decreased tPA and increased M2 histiocytes producing XIIIA, which could in part explain the development of CRSwNP.

A detailed study of cytokine expression in CRS has been carried out by Hulse et al. [28] suggesting a central role of Type 2 cytokines, IL-5 and IL-13 in polypogenesis. Type 2 cytokines may be synthesised by type 2 innate lymphoid cells, Th2 lymphocytes, mast cells or basophils [29]. Antibodies targeting IL-5 and the alpha chain of the receptor for IL-4 and IL-13 have been demonstrated to lead to polyp shrinkage by Bachert et al. [30] and Gevaert et al [31] IL-13 induces synthesis of VCAM-1 in the capillary endothelium, thus promoting lymphocyte, eosinophil and basophil extravasation. IL-13 also promotes the epithelial expression of C-C motif chemokine receptor 3-specific chemokines that draw mast cells, eosinophils and basophils into the polyp tissue. Other molecules of significance are the C-C motif chemokine ligand 13 (MCP-4/CCL13) and eotaxins-1, 2, and 3 [21]. Eosinophil persistence and activation within tissues are promoted by IL-5 [32]. When mast cells are set into action, they cause goblet cells to release mucus and glands to secrete serous products. IL-13 acts on monocytes to transform into the activated M2 histiocyte type. Eosinophils synthesise chemokine (C-C motif) ligand 23 (CCL23), and this molecule is markedly raised in polyps [33]. CCL23 attaches to CCR1 and assists in M2 histiocyte activation. As noted above, IL-13 inhibits the production of tPA and has a role in fibrin mesh formation. Only nasal polyps where type 2 inflammation occurs may show M2 histiocytic activation, fibrin mesh formation and IgE activity [34].

B-cell activation with excessive local antibody production is characteristic of CRSwNP [1]. Polyps express B-cell activating factor (BAFF), which induce antibody production, isotype class switching to IgE and IgA and the development of autoimmune immunoglobulins [1]. Tan et al. detected increased anti-dsDNA IgG and IgA autoantibodies in nasal polyps, suggesting a role for autoimmunity in severe CRSwNP [35]. This research utilised ELISA to search for class-switched autoantibodies in tissue taken from polyps as well as from different parts of the nose (the inferior turbinate and uncinate process). The researchers concluded that autoantibodies of the IgG and IgA type were present in nasal polyps, especially the former and reacted against several test antigens. Kato et al. [36] noted the predominance of autoantibodies to epitopes located within the nucleus (anti-dsDNA). Anti-dsDNA autoantibodies are key to the pathogenesis of a number of autoimmune disorders, e.g. systemic lupus erythematosus (SLE). However, the raised levels of anti-dsDNA antibodies were not reflected in an increase in serum levels of IgG. The autoreactive immunoglobulins were only found in nasal polyps, not elsewhere in the nose, nor even in the inferior turbinates of CRSwNP cases.

Increased number of histiocytes have been detected in the vicinity of the middle turbinate surrounding the polyp, which may indicate aberrant host defence during the development of CRSwNP [25]. The fibrosis observed implies the formation of a containing band of collagen, which inhibits bacterial spread and prevents the development of a broader oedematous inflammatory reaction [25]. In terms of the sequence of pathological processes, these appear to occur alongside each other, rather than sequentially. Taken together, CRSwNP has been characterised by several inflammatory processes such as epithelial injury, attempts at repair, recruitment of eosinophils and macrophages, remodelling and production of fibronectin, which together with dysbiosis or other environmental insults likely results in the development of a polyp [37, 38].

35.3 New Immune-Modulators and the Treatment of Nasal Polyposis

The pathophysiology of nasal polyp formation depends on complex interactions between the sinonasal barriers and immune system, which sustain chronic inflammation. The molecules orchestrating these inflammatory events are important targets for the development of novel therapeutics of CRSwNP [39].

Type 2 inflammatory responses share many features in common, including the involvement of eosinophils and the expression of type 2 immune modulators, such as IL- 4, 5, 9 and 13 by Th2 lymphocytes and ILC2 cells. These modulators are found both in polyp and in peripheral blood samples [40]. Other modulators which can provoke or sustain type 2 inflammation are IL- 25, 31 and 33 and thymic stromal lymphopoietin (TSLP), produced by epithelium [41, 42]. The basic treatment of CRSwNP is intranasal corticosteroids. In severe CRSwNP, systemic short-term corticosteroid courses may additionally be considered, yet side effects are possible [43]. Corticosteroids decrease eosinophilic involvement and improve barrier functions. A study group showed that fluticasone propionate prevented IL-4-induced nasal epithelial barrier dysfunction in vitro and allergen-induced mucosal permeability in a murine model [44]

After failure of basic pharmacotherapy surgery of CRSwNP may be considered, endoscopic sinus surgery (ESS) targets to remove nasal polyps in order to improve the intranasal penetration of intranasal corticosteroids. ESS also aims to restore osteomeatal function by widening the natural ostia of paranasal sinuses. ESS reduces nasal obstruction, facial pain and nasal discharge, yet surgery's effect on restoring the sense of smell is less good [21, 45]. The proportion of CRSwNP patients developing relapse after ESS has been estimated to be up to 80% within a 12-year period, and a revision ESS is performed in 37% of cases [46]. Thus, severe and recurrent CRSwNP still lacks efficient management.

Biological therapeutics for asthma and/or CRSwNP are monoclonal antibodies. They usually are targeted to Type 2 inflammatory molecules: omalizumab (anti-IgE), mepolizumab and reslizumab (anti IL-5), benralizumab (anti IL-5 receptor) and dupilumab (anti IL-4 receptor alpha). Omalizumab is a novel biological agent,

the target of which is IgE. It is a recombinant humanised monoclonal immunoglobulin (mAb). It targets IgE and prevents binding to the high-affinity FcεRI receptor on certain cell types, notably mast cells, eosinophils, basophils and dendritic antigen-presenting cells (DAPCs) [47–49]. By binding to IgE, the IgE can no longer stimulate the receptor. Thus, both circulating IgE fall, and there are fewer FcεRI receptors expressed on cell membranes. Interactions between IgE and the high-affinity receptor are minimised, and the release of pro-inflammatory signals declines. In the longer term, the FcεRI receptor expression is greatly reduced on mast cells, basophils and DAPCs [48, 50], followed by a similar downregulation on effector cells. Omalizumab has been demonstrated to reduce symptoms in both the proximal and distal airway in individuals suffering from CRSwNP and asthma. It also reduced nasal polyposis as assessed endoscopically and led to a reduction in subsequent pharmacotherapy or operative interventions [51, 52]. Pinto et al. [53] researched the use of omalizumab in cases of persistent sinusitis, usually with polyposis, and compared the results against placebo administration. There was no restriction on concomitant medication use; thus, omalizumab was assessed as an adjuvant treatment. The group receiving active agent exhibited significant reductions in sinusal inflammation evaluated by CT imaging. The placebo recipients did not have similar changes. Intergroup comparison for the size of change gave a statistically insignificant result, however. Gevaert et al. investigated endoscopically obtained polyp score changes in cases of CRS with concomitant asthma [54]. The groups were classified as atopic or non-atopic depending on the results of skin prick testing. Other medications (steroids (both oral and topical), topical decongestants, antimicrobials and leukotriene receptor antagonists) were forbidden. The atopic group had statistically meaningful improvements in endoscopically evaluated polyposis scores, and these were confirmed by CT imaging. This improvement, somewhat surprisingly, also occurred in the non-atopic individuals. Omalizumab has also been investigated in terms of adverse events profile and anaphylaxis post-injection was noted in 0.09% of cases [55]. There are at present several candidate anti-IgE biological therapies in safety and efficacy testing. Two agents, in particular, are under development: ligelizumab [56], a monoclonal antibody vs IgE, the binding affinity of which is even higher than omalizumab, and quilizumab [57], a monoclonal antibody which attacks the M1 epitope on membrane-bound IgE.

One of the other principal targets for novel therapeutic agents to target is interleukin 5. This cytokine is an important mediator in the development of Type 2 (eosinophilic) inflammatory reactions. An agent targeting IL-5 could be beneficial in managing chronic disorders of the proximal airway. IL-5 orchestrates the production, development and recruitment of eosinophils, both in the bone marrow and in the airways [58]. Two monoclonal humanised anti-IL-5 recombinant antibodies that can target IL-5 and have acceptable safety and tolerability in patients with intranasal polyps are mepolizumab [59] and reslizumab [60]. When these agents are halted, rebound eosinophilia has been noted, but this does not appear to cause significant worsening of symptoms [57]. Nonetheless, to ascertain the ideal dosage regimens in clinical practice, there is a need for research involving more individuals with longer periods of therapy and follow-up [60]. Humanised monoclonal recombinant

antibody benralizumab targets the abundant interleukin 5 receptor (IL-5Rα) on eosinophils and has been shown to be effective in severe asthma [61]. Yet its effect has not been assessed in CRSwNP.

Two other potential targets are interleukins 4 and 13, which play key roles in the synthesis of IgE and Type 2 inflammatory responses. Both these mediators act upon the same receptor—IL-4Rα [62]. A completely human monoclonal antibody does exist which targets this receptor—dupilumab [63]. Phase 3 trial of severe CRSwNP showed that dupilumab lead to polyp shrinkage, improved obstruction and decreased need for peroral corticosteroids [64]. There were fewer reported adverse events in the dupilumab group compared to placebo group [64].

35.4 Conclusions and Future Needs

Despite many investigations, the pathogenesis of CRSwNP has not yet been resolved. CRSwNP results from a combination of environmental stressors, genetic susceptibility and events leading to barrier penetration. This might result in a chronic inflammatory response that utilises Type 1, 2 or 3 pathways. Majority of Western CRSwNP patients exhibit Type 2 cytokine profile (of such as IL-4, IL-5, IL-13) and eosinophilia. The knowledge of antigens triggering CRSwNP is still limited, although some common nasal bacteria, including *S. aureus*, have been proposed to result in host immune reactions in CRSwNP. Biological therapeutics represent a new approach to manage severe and progressive CRSwNP not responding to or having contraindications to conventional therapy such as corticosteroids and/or endoscopic sinus surgery. The challenges of biological therapeutics include their high development and production costs reflecting their high treatment costs. Still, several new biological therapeutics are under investigation or already in use for CRSwNP.

Recent analysis has shown that ESS is more cost-effective than the only currently licensed biological, dupilumab, even when revision surgery is needed. The ESS strategy cost $50,436.99 and produced 9.80 QALYS; using dupilumab cost $536,420.22 and produced 8.95 QALYs. If dupilumab was priced above $855 per year, then ESS was more cost-effective [65].

The ESS strategy cost $50,436.99 and produced 9.80 QALYs. The dupilumab treatment strategy cost $536,420.22 and produced 8.95 QALYs. Because dupilumab treatment was more costly and less effective than the ESS strategy, it is dominated by ESS in the base case. One-way sensitivity analyses showed ESS to be cost-effective versus dupilumab regardless of the frequency of revision surgery and at any yearly cost of dupilumab above $855.

A future need is to find cost-effective biomarkers for endotyping CRSwNP in order to provide individualised management. There is also a need to explore which patients benefit the most biological therapeutics, as well as to compare different therapies of CRSwNP. Increased evidence-based knowledge of CRSwNP has been taken into account in new treatment algorithms in EPOS 2020. Yet, a future challenge is to make a consensus algorithm of patient selection, timing and treatment details (including surgery). Finally, current management is rarely able to lead to

total remission of CRSwNP. Hence, a deeper understanding of the development of CRSwNP is still needed, and this may in the future provide new therapeutic targets or possibilities of early prevention of CRSwNP.

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The Importance of IgE and the Uses of Anti-IgE

36

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36.1 Introduction

Immunoglobulin E (IgE) is key to the development of allergic disorders, such as allergic asthma [1]. Given this centrality, for many years, manipulation of the elements of the immune system that are linked to IgE function has been a desirable goal in the treatment of asthma and other allergic disorders [2].

Systemic IgE levels are raised in the majority of allergic asthma sufferers, once age adjustment has been performed [3]. The patient becomes sensitised to an allergen when specific IgE (sIgE) is formed to epitopes found on inhaled allergens such as house dust mite, pollen, animal dander, fungi or cockroaches [1]. Food allergens may also be relevant, especially in children.

B cells synthesise IgE under the influence of two similar signalling molecules, interleukin 4 and interleukin 13 (IL4 and IL13). These two cytokines are synthesised by a variety of types of cell, amongst others, the T helper 2 (Th2) cells which are the T helper cell variant most implicated in atopic disorders [4, 5]. An atopic disposition is the highest risk factor in the development of allergic asthma [3, 6, 7]. Allergies are found in approaching 80% of asthma sufferers in the United States or

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_36

the developed world, as shown by the positivity of skin prick testing for at least one antigen and serological evaluation for sIgE to particular antigens [2, 8, 9].

36.2 How Important Is IgE in IgE-Mediated Allergic Diseases?

Allergic disorders have complicated pathogenesis. Clinically, allergic disorders fall into two categories: those that involve IgE and those that occur through other innate immune mechanisms. Atopic disease involves cellular inflammatory components (mast cells and basophils, amongst many others) and molecular inflammatory components, such as the cytokines (an example of which is IL4) and soluble mediators, including histamine [10]. IgE, a type of immunoglobulin that is uniquely mammalian, has features found only in this isotype and is a key component of IgE-mediated allergic disorders. IgE usually has the lowest concentration of the immunoglobulins. Circulating IgE levels in health are around 150 ng/mL, IgG levels being far higher at 10 mg/mL [11]. Circulating IgE has a half-life of around 3 days but may persist for up to 6 weeks when cell-bound. Circulating IgG has a half-life of 20 days [11].

The levels of sIgE increase when exposed to the corresponding allergen. IgE exists in two forms: unbound IgE, which is synthesised by plasmacytes, and bound IgE expressed on the plasma membrane of B lymphocytes during class switching [12, 13]. IgE has a make-up that resembles the other immunoglobulin isotypes, i.e. two heavy chains that are the same and two light chains that are the same. The heavy ε-chain in IgE has an additional domain not found on IgG. IgE has Cε3 and Cε4 domains that possess sequence homology with the Cγ2 and Cγ3 domains found on IgG and have a structural similarity. In IgE, two Cε2 domains replace the flexible hinge region of IgG and are the main structural difference between IgE and the other isotypes [14–16]. The Cε2 regions of the molecule can twist back on themselves to touch the Cε3 and Cε4 regions. In this way, the Cε2 domain may provide space between the Fab (antigen-binding fragment) arms and Fc (crystallisable fragment) portions of IgE. When the Cε2 regions have folded upon themselves, they confer the ability on IgE of adopting various conformations [13].

IgE has a central part of how allergic disorders begin and how they subsequently develop. IgE functions by attaching to its corresponding receptor present on mast cells and basophils. IgE functions in defence against parasitic worms (helminthic species) and assists in disposing of alien substances that enter the body, such as poisons, venoms, irritant substances and xenobiotics [17]. On the first contact with an antigen, IgM immunoglobulins, synthesised by plasma cells derived from B lymphocytes are replaced by IgG, then IgE following class switching [10]. B lymphocytes producing IgE then mount a response by releasing unbound IgE into plasma, which interacts with the FcεRI molecule, a receptor possessing a high affinity for IgE and expressed by mast cells and basophils [18]. This mechanism produces sensitisation, whereby subsequent contact with the antigen leads to the binding of membrane-bound IgE on mast cells to their epitopes. When this occurs, mast cells degranulate and step up production and secretion of the multiple molecules found in

allergic reactions (e.g. histamine, the leukotrienes, platelet-activating factor), both local and generalised [19].

Anti-IgE treatment leads to reductions in the number of IgE receptors on the membrane of effector cells. High levels of IgE increase the expression of the FcεRI, as well as the FcεRII, receptor, and lowering IgE through therapy means the receptors will also decrease [20, 21]. Membrane-bound IgE can stimulate the CD79A plus CD79B (also called Igα and Igβ) molecules, which cause B lymphocytes to proliferate and form plasmacytes [22].

36.3 IgE-Targeted Treatment for Allergic Disorders

Treating atopic disorders by techniques or agents that can modulate the IgE-associated molecular pathways safely and with both efficacy and convenience is an appealing prospect to many researchers [12]. IgE itself represents a key target in atopic pharmacotherapy. The principal approach has been to bind free IgE circulating in the bloodstream and thereby stop the activation of IgE receptors on effector cells. This approach means that both early and late phases of the allergic response can be prevented [12].

36.3.1 Anti-IgE Therapy: *Omalizumab*

Omalizumab is a recombinant humanised monoclonal antibody against IgE that has been created by the Novartis Pharmaceutical Company [23]. Its mode of action is to affix to the Cε3 region of the Fc portion of the heavy chain on unbound IgE, resulting in a significant decrease in unbound IgE [24]. The same domain bound by omalizumab normally allows IgE to stick to the alpha chain of the IgE receptor. In this way, IgE can no longer bind to FcεRI, and thus, mast cells or basophils do not release their granules, and the inflammatory cascade is halted [25]. When IgE binds to FcεRII on the B lymphocytic membrane, increased binding of antigen ensues, and the Th2 cells are stimulated into action. Omalizumab works, therefore, by both preventing IgE from binding and presenting allergens and stopping the recruitment of the Th2 cells that orchestrate inflammation [26].

Nonetheless, use of omalizumab is not without problems. The agent lowers IgE levels gradually, necessitating therapy on a continuous basis for a prolonged period, lasting a number of weeks [27]. The US Food and Drug Administration (FDA) considers that prolonged use of omalizumab makes a thrombotic event within an artery marginally more probable and may adversely affect the cardiac and cerebral vascular supply [28]. Due to the high cost of prescribing omalizumab for a prolonged period, the agent finds most use in severely asthmatic individuals [29]. Patients with persistent spontaneous urticarial also benefitted from a 12-week course of omalizumab, with a swift decrease in numbers of FcεRI molecules and sIgE on basophils found in the systemic circulation [30].

36.3.1.1 Omalizumab Therapy in Asthma

Omalizumab is a recombinant humanised IgG1 monoclonal antibody. It targets IgE with high specificity and is intended for use in allergic disorders [31–34]. The sole anti-IgE treatment licensed in asthma at present is omalizumab [2].

The licence for omalizumab includes cases where all of the following stipulations apply [35, 36]:

- *The patient must be at least 6 years old.*
- *In the United States, chronic asthma of moderate to marked severity.*
- *Inhalational steroid therapy has failed to control symptoms (in the United Kingdom, add: patient remains symptomatic despite large dosage of inhaled steroids).*
- *Serological titre of total IgE must be above 30 and lower than 700 international units/mL in adults and below 1300 IU/mL in cases aged 6–11 years (1500 IU/mL in Europe). These ranges cover the concentrations at which omalizumab can lower IgE to a level where clinical benefit ensues, as long as the recipient has a weight in the target range.*
- *There is evidence of the patient being sensitised to a perennial antigen, as seen on skin prick testing or sIgE serology. Such antigens include house dust mites, animal dander, fungi or cockroaches.*

Mechanisms of Action

Omalizumab attaches to IgE at the point where IgE usually binds to FcεRI and FcεRII on mast cells, basophils and certain other cells, i.e. Cε3, the third constant region on the heavy chain portion. Circulating IgE cannot therefore bind to its receptor. The complex formed between omalizumab and sIgE is removed from the circulation within the reticuloendothelial system. Omalizumab possesses specificity for IgE and is unable to interact with the other isotypes (G and M). A key feature of the pharmacological mechanism is that there is no affinity of the agent for IgE receptors, nor can it target IgE already bound to receptors. In this way, IgE bound to cell membranes is unaffected, and there is no inadvertent activation of mast cells/basophils [2, 37].

Efficacy

Omalizumab has been proven to have greater efficacy vs. placebo in reducing the frequency of asthmatic exacerbations and in lowering steroid requirements (via inhaler or by mouth) in cases of asthma of moderate to marked severity [38–41]. Up to the present, no trial has made a head-to-head controlled comparison of omalizumab vs. other treatments for asthma, e.g. steroid inhaler plus long-acting beta agonist, leukotriene antagonists or allergen-specific immunotherapy [2].

Route of Administration

The licensed route of administration for omalizumab is subcutaneous injection. Early clinical testing showed that inhaled omalizumab had no protective effect in challenges of allergen, nor did it change systemic IgE levels [42].

36.3.1.2 Omalizumab Therapy in Chronic Urticaria

Randomised trials have been conducted, which demonstrated that omalizumab has benefit in both spontaneous urticaria following failed guideline-directed treatment and for certain variants of inducible urticaria. The agent was licensed in 2014 in the United States for the indication of persistent spontaneous urticaria in adults and teenagers which has continued to produce symptoms even after administering H1 blockers. In the United Kingdom, the National Institute for Clinical Excellence (NICE) rules for use are stringent:

- *"Omalizumab is recommended as an option as add-on therapy for treating severe chronic spontaneous urticaria in adults and young people aged 12 years and over only if:*
- *The severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more.*
- *The person's condition has not responded to standard treatment with H1-antihistamines and leukotriene receptor antagonists.*
- *Omalizumab is stopped at or before the fourth dose if the condition has not responded.*
- *Omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses.*
- *Omalizumab is administered under the management of a secondary care specialist in dermatology, immunology or allergy.*
- *The company provides omalizumab with the discount agreed in the patient access scheme."*

The dose differs from that given in asthma and is 150 mg or 300 mg administered subcutaneously once each month, without reference to circulating IgE titre or body weight [2].

36.3.1.3 Omalizumab in the Treatment of Other Allergic Disorders

Reports suggest benefit from using omalizumab in food allergies, nasal polyp formation, essential anaphylaxis, allergic rhinitis, allergy to venoms, allergic eczema and a number of other conditions [2].

There have been trials of omalizumab and similar agents acting as anti-IgE immunoglobulins, in treating food allergy (including paediatric cases where immunotherapy was provided by mouth), nasal polyp formation, bullous pemphigoid, asthma associated with eosinophilic granulomatosis with polyangiitis (formerly termed Churg-Strauss syndrome), and allergic bronchopulmonary aspergillosis [43–51]. Use of omalizumab in such indications may be outside licensed dosage ranges, as sufferers from these disorders may have exceptionally raised IgE titres outside those used in calculating the licensed doses [2].

Omalizumab Treatment for Allergic Rhinitis

In vitro experiments have revealed that circulating leukocytes from allergic rhinitis sufferers exposed to anti-IgE secrete lower levels of leukotrienes after exposure to

allergens, indicating that effector cells secrete fewer inflammatory mediators following contact with anti-IgE [52]. When tryptase levels in secretions from the nose were measured, as an indicator of mast cell activation, individuals who had received anti-IgE had less tryptase release than those given placebo [53]. Circulating eosinophils and nasal eosinophils were less abundant in individuals administered omalizumab for allergic rhinitis than those given placebo, following contact with pollen allergens. Circulating and local eosinophil numbers and serological unbound IgE titres were significantly correlated [54]. A partial explanation for this situation is that omalizumab inhibits recruitment of the mast cell response and secretion of certain mediators (such as interleukin 5) and thus impairs chemotactic attraction of eosinophils towards the nose [55, 56].

To suppress unbound IgE to a level where detection is difficult, the omalizumab dose needs to be around 10–15 times higher than that of the combined bound and unbound IgE that is being targeted. This is the reason why the dosing amount and interval need to be calculated on the basis of the total serological IgE titre at the beginning of therapy and the body weight. Omalizumab usually reaches its steady-state concentration 14–28 days after injection, whether subcutaneous or intravenous. Following repeated administration of omalizumab by subcutaneous or intravenous injection, the drug is slowly cleared, the average half-life being 2.9 weeks. The highest concentration of the drug is in serum. The drug is not deposited at a particular organ site, nor are anti-omalizumab antibodies detectable [55, 57].

Research by Ädelroth et al. [58] involved 251 individuals who were suffering from allergic rhinitis secondary to birch pollen. They were administered either omalizumab or placebo whilst birch pollen was in season. The dosage followed the recommendations given by Casale et al. [59]: 300 mg subcutaneous injection twice in 1 month if the pretreatment IgE serological titre was 150 IU/mL or lower or three times at 3-week intervals where the pretreatment titre was above 150 IU/mL. The group receiving active treatment scored better on mean severity of daily nasal symptoms, used less medication alongside omalizumab and had a better rhinitis-related quality of life than the placebo group. The group receiving active treatment had serological titres for unbound IgE that were greatly lower than the placebo group, and the titre had an association with markers of clinical efficacy. Omalizumab produced no toleration issues, and no antibodies to the agent were detectable. Regrettably, at the time of the study beginning, the birch pollen was already airborne and thus present when the first doses were given (or before). This timing may have obscured some actual benefit from the agent [55] which was less effective than intranasal corticosteroids when trials were compared. The number needed to treat (number of patients treated with a drug needed to make one person better) was 12.4 for omalizumab and 4.4 for nasal corticosteroids [60].

Omalizumab Treatment of Nasal Polyps

Experimental studies have shown that basophils possessing sIgE, when exposed to enterotoxin B, degranulate [61]. Therefore, sIgE to enterotoxin found on mast cells within polyps may play a role in polyposis by leading to degranulation, just as is expected for sIgE targeting inhaled aeroallergens. Given that there are so many

clones, there are potentially hundreds of antigens which may cause ongoing degranulation by mast cells, as seen in nasal polyps. This is the rationale behind the use of anti-IgE in treating persistent or repeated nasal polyp formation or non-allergic asthma when severe in degree, namely, to inhibit the developing inflammation by targeting pathways dependent on IgE. Penn and Mikula [46] analysed two sets of individuals with allergic asthma and polyp formation in the nose, who were treated endoscopically. The researchers evaluated the benefit after surgery of using omalizumab in four patients vs. four controls without omalizumab. The evaluation included sinus CT imaging and nasal endoscopy. CT scoring was the same in both groups, but omalizumab led to better scores on an assessment of nasal polyposis. Within the eight patients overall, the serological titre for IgE correlated with how severe nasal polyps were [46].

These results may need to be interpreted cautiously since the method by which the patients are selected may influence the outcome. A raised level of IgE within polyps is not reflected in the positivity of cutaneous allergy testing, unlike the case with allergic rhinitis. Locally distributed IgE within polyps is frequently no indicator of serological titres for circulating IgE, a fact which complicates how patients are selected for trials. Indeed, the concentration of sIgE at one anatomical locale may be markedly raised (more than 1000 kIU/L), such that it would be hard to achieve a sufficient anti-IgE concentration to be effective, yet the circulating levels of sIgE may be low, encouraging clinicians following current recommendations to administer an insufficient dose of omalizumab. Provided that treatment led to improvement, the basic principle that anti-IgE is beneficial for nasal polyposis would be supported, and omalizumab could then be employed in both cases of nasal polyp formation and potentially non-allergic asthma of a marked degree [55]. Further details of anti-IgE in nasal polyposis are in Chap. 35.

36.3.1.4 Adverse Effects of Omalizumab

Hypersensitivity to anti-IgE may manifest as anaphylaxis, hives or inflammation at the site of injection. A hypersensitive response of severe degree to omalizumab or any component thereof is a contraindication to the use of anti-IgE [2]. Caution is needed in patients who have had cancer or parasitic infections. Anti-IgE should not be used in pregnancy nor during breastfeeding as it crosses the placenta and can also enter breast milk.

The frequency of anaphylactic or anaphylactoid responses that seem to be uniquely tied to omalizumab use is around 1 or 2 patients in 1000 of those taking the drug [62–65]. Anaphylactic reactions may occur at any point in dosing. A study reviewing 124 occurrences of anaphylaxis discovered that 39% happened after the initial dose, and 19% happened after the second administration. About 68% of reactions did not occur until after 3 doses had been given [62]. Around 70% of the reports of anaphylaxis give a timescale of less than 2 h after the dose was provided, but there are other reports with timescales of up to 4 days post dose administration, and anaphylaxis has, on occasion, persisted for 1–2 days [66, 67].

It is feasible to carry out skin prick testing to assess the likelihood of an anaphylactic reaction being linked to omalizumab, but it is unknown how well this test

predicts a reaction. Prick tests can utilise the agent as is, but intradermal testing may be better when the drug is dissolved in normal saline. A concentration of 1:100,000 (1.2 micrograms/mL) is known not to cause local irritation [68].

36.3.2 Cost-Benefit Analysis

A Japanese study found that omalizumab was not cost-effective with an incremental cost-effectiveness ratio (ICER) for add-on omalizumab compared with standard therapy alone was US $755,200 (95% credible interval (CI) $614,200–$1,298,500) per quality-adjusted life-year gained. The ICER was 22% lower in a responder subgroup [69]. In the United States, omalizumab was also found not cost-effective, with an ICER of $491,000 per QALY gained even in patients with five times the baseline acute event rate [70].

It is very important for clinicians to consider all other possible options before using very expensive monoclonal antibodies in respiratory disease. Such therapies should be reserved for those with severe, unresponsive, quality-of-life-destroying or life-threatening conditions.

36.3.3 Other Therapies to Reduce IgE

36.3.3.1 Higher-Affinity Anti-IgE: *Ligelizumab (QGE031)*

Ligelizumab, which, like omalizumab, underwent development at Novartis, is a humanised monoclonal immunoglobulin with antigen specificity for the third constant domain of IgE [71]. Similarly to omalizumab, ligelizumab prevents IgE from attaching to mast cells or basophils. In this way, it inhibits the inflammatory pathways linked to IgE and is efficacious in the management of atopic disorders linked to IgE function. In phase 2 clinical trials, where the pharmacodynamic and pharmacokinetic properties of ligelizumab were investigated alongside safety aspects, ligelizumab demonstrated greater efficacy in lowering IgE concentrations than omalizumab. It achieved this by blocking the interaction of IgE with the FcεRI receptor. Superior results were also achieved when cutaneous testing was used as outcome measure [72, 73]. It is thus anticipated that ligelizumab will be a valuable agent in the future for use in atopic disorders. Part of the explanation for the superiority of ligelizumab is that it binds to IgE with 50 times the avidity of omalizumab [73, 74].

Field trials of ligelizumab in asthmatic patients have failed to demonstrate superiority to omalizumab; hence, the agent is no longer being tested for this possible indication. It is, however, still undergoing assessment as an agent for use in persistent spontaneous urticaria [2].

Quilizumab [75], a monoclonal antibody which attacks the M1 epitope on membrane-bound IgE, is also under investigation as means of decreasing production of IgE.

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When Should We Use Biologics in Rhinology?

37

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37.1 Biologics

Biologics (also known as biologicals, biological products, or biopharmaceuticals) are a specific group of drugs. The World Health Organization defines a drug as "a substance or product that is used to modify or examine physiological systems or pathological conditions for the benefit of the individual." In one aspect, the term drug refers to a pure chemical substance that is used in medicine and has a biological activity (bioactive), or it could also be a natural mixture containing a standard amount of active substance of plant or animal origin [1–3]. Drugs generally have well-defined chemical structures and can often be analyzed to determine their components [4]. Unlike conventional chemically synthesized drugs, biologics are produced or extracted in a living system such as a microorganism, human, plant, or animal and contain glucose, protein, nucleic acid, or a combination thereof, and sometimes living cells or tissues. Biologics are usually composed of large complex molecules and are also created as copies of existing structures such as antibodies or hormones [5–7].

Chemically synthesized drugs are unlikely to be contaminated and are easy to protect from contamination. It is also important that the final products of biologic drugs are sterile and pure at acceptable levels without the presence of biological

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_37

structures such as prions, viruses, bacteria or host-source proteins, DNA/RNA, or cellular residues [8].

The term immunogenicity, defined as the ability of a substance, such as a protein or an allergen, to trigger a wanted (e.g., vaccines), unwanted (e.g., monoclonal antibody), or unanticipated immune response or reaction, is the most important safety criterion of biotechnological and biosimilar drugs. In general, biotechnological drugs can produce an immune response in the body because of their large and complex structure. They may also cause an immune response in the host (treated) organism as a result of uncontrolled structural deviations in the product or as a result of degradation of the purity and sterility of the product during production, storage, and transport [6, 9–14].

Biologic drugs are immunogenic, even if they are fully human monoclonal antibodies. Antidrug antibodies may reduce the activity of biologics and/or cause side effects. Additionally, reactions such as cytokine release syndrome, immune complex hypersensitivity, serum disease, autoimmune hemolysis, mast cell activation, and fatal anaphylaxis may also develop [15, 16].

Optimized treatment regimens (drug dose, frequency, and immunosuppressive splicing) can minimize the development of antidrug antibodies and enable us to effectively cope with immunogenicity against biologic drugs [17] (Table 37.1).

Table 37.1 Comparison of chemical and biological drugs

	Small-molecule drugs (chemical-based)	Biological drugs (protein-based)
Example	Aspirin	Omalizumab
Molecular weight	180 Da [18]	140,000 Da [19]
Structure	Simple and well defined [9]	Complex (size and three-dimensional structure) [13]
Synthesis	With controlled and predictable chemical synthesis [13]	Manufactured in a living cell line (various methods such as multistage isolation and purification are used in production) The product is unpredictable due to reasons such as inherent diversity, heterogeneity, randomness, and immunogenicity [8, 13, 20]
Characterization	It can be entirely characterized by analytical methods [9, 21]	It is difficult to fully characterize by analytical methods
Stability	Stable They are not affected by changes in the environment such as agitation, mixing, heating, drying during production, postproduction, transportation, and storage [9, 22]	Unstable The stability and integrity of biologicals are influenced by environmental conditions during storage and transport. They are more sensitive to heat and microbial contamination under storage conditions [6, 9, 22]
Immunogenicity	It is not usually seen or expected	It has a high potential. Must be tested during development

References [6–9, 13, 18–22]

37.2 Categories of Biologics

The US Food and Drug Administration's (FDA) Center for Biological Evaluation and Research (CBER) was responsible for the evaluation and regulation of therapeutic biological products from 1987 to 2003. However, in 2003, a group of biological products was transferred to the Center for Drug Evaluation and Research (CDER) [23, 24].

Biological products under the direction of the CBER have been categorized as blood and blood products, tissue and tissue products, vaccines, allergenic extracts (e.g., allergy test, immunotherapy), xenotransplantation, and cellular and gene therapy products [5, 23–25].

Biologicals produced by biotechnology methods that are affiliated to the CDER are categorized as (under the *FDC Act* and/or the *PHS Act*, as appropriate) monoclonal antibodies, cytokines, growth factors, immunomodulators, and enzymes [5, 23, 24, 26].

37.3 The Historical Development Process of Biologics

The development and use of biotherapeutic agents began with the discovery and isolation of the gene in the 1970s and gained rapid momentum after the development of recombinant DNA technology and the approval of the first product, Humulin (1982), by the FDA [27]. The first therapeutic antibody was developed as a humanized chimeric protein containing a majority of mouse or other xenobiological portions. This led to an increase in efficacy, tolerance, and safety for patients [28].

After the approval of Humulin, a total of 91 recombinant protein-based new molecular structures were therapeutically approved by the FDA. These biologic drugs can generally be grouped as monoclonal antibodies, modulators, or replacements of enzymes and receptors [27]. The first FDA-approved drugs in these three categories (with company and year) were rh insulin (Eli Lilly, 1982) as the receptor modulator, muromonab CD3 (Ortho, 1982) as the monoclonal antibody, and Dornase alpha Genentech (1993) as the enzyme modulators.

Between 1982 and 2013, a total of 91 biological drugs (31 receptor modulators, 34 monoclonal antibodies, 26 enzyme modulators) and 777 small molecule drugs were approved. The approval period for these new drugs was 8.5 years for small molecule drugs and 7.4 years for biologics. The approval period of biologics was 7.8 years for monoclonal antibodies, 5.9 years for enzyme modulators, and 8.3 years for receptor modulators. While 3.3% of small-molecule drugs were withdrawn due to safety concerns, this rate was 2.2% for biologics. Studies comparing small-molecule drugs and biological-based drugs have shown that biologics have shorter development and approval times and are generally safer. The target disease groups of the biologics are metabolic, cardiovascular, and infectious diseases, especially oncology and autoimmune/inflammatory diseases [27].

As information regarding the key molecules, inflammatory pathways, and regulatory processes in the underlying pathophysiological mechanisms of allergy and

immunology diseases increases, the effective use of biologics in the treatment of these disease groups will also increase [29].

Information on the use of biologics in allergic diseases was obtained from asthma studies [30]. Biologics modify type 2 inflammation by blocking cytokines such as Ig E, IL4, IL5, and IL13. In selected patient groups of diseases with type 2 inflammation such as chronic rhinosinusitis with polyps, severe atopic dermatitis, chronic urticaria, and hypere osinophilia syndrome, antagonist biologics may be useful [29]. Studies have shown that the rational and informed use of biological agents is safe and effective, and these agents can be used in the treatment of patients who do not respond to current treatment methods as well as to reduce the risk of side effects [31–34].

37.4 Biologics in Rhinological Diseases

37.4.1 Allergic Rhinitis

Allergic rhinitis (AR) is a disease characterized clinically by symptoms caused by immunologically mediated inflammation (most often type-I IgE-mediated hypersensitivity) in the nasal mucosa after contact with the allergen [35].

37.4.1.1 Omalizumab

Omalizumab is a recombinant human monoclonal anti-Ig E antibody administered subcutaneously. It reduces the level of free IgE by binding to the Fc portion of the free-circulating IgE antibody and prevents IgE from binding to high-affinity IgE receptors. It also reduces the expression of high-affinity IgE receptors on mast cells and basophils. It provides a significant reduction in the number of eosinophils, lymphocytes, and other inflammatory cells in the respiratory tissue [36–38].

Omalizumab was approved for the treatment of severe allergic asthma by the FDA in 2003 and the European Medical Agency in 2005. Omalizumab is not currently approved by the US FDA for the treatment of AR alone.

In a meta-analysis, it was reported that the use of omalizumab in moderate-severe AR patients, which could not be controlled by conventional treatment, produced a significant reduction in symptom scores and the need to use other symptomatic drugs and also improved quality of life [39]. In studies that used omalizumab with allergen immunotherapy in the treatment of seasonal AR, it has been reported that symptom scores and the need to use rescue medication were reduced [40].

Starting omalizumab treatment 9 weeks before allergen immunotherapy significantly reduces serious side effects and anaphylactic events related to immunotherapy [41]. Omalizumab may support the development of tolerance during immunotherapy by lowering the level of free serum IgE [42]. Although the combination of omalizumab in the first year of immunotherapy reduces symptom scores and the need to use other symptomatic drugs, its effect does not persist in the long term [43]. According to current data, omalizumab is considered as a new therapeutic

agent, especially in patients with moderate to severe AR who have allergen-specific antibodies and do not respond to conventional pharmacotherapy. Also, omalizumab may be useful in patients with AR and asthma. However, the drug is not FDA approved for AR alone, and the cost of therapy is a very important factor [42]. Omalizumab is generally well tolerated, with few serious adverse effects. Local reactions at the injection site, viral infections, sinusitis, headache, pharyngitis, and rarely urticaria, anaphylaxis and anaphylactoid reactions, thrombocytopenia, and alopecia have been reported. In controlled studies on the potential for malignancy, no difference was found between the groups receiving and without omalizumab treatment [44].

The ARIA group recommends omalizumab in patients with AR and asthma with an obvious IgE-dependent allergic component that cannot be controlled despite optimal pharmacological treatment and appropriate allergen prevention. There are no recommendations for the use of anti-Ig E in patients with AR without asthma [45].

37.4.2 Chronic Rhinosinusitis

In some chronic rhinosinusitis patients with nasal polyps (CRSwNP), marked eosinophil infiltration, IL5 secretion, and IgE production are observed with T helper 2 cell polarization, whereas in patients with chronic rhinosinusitis without polyps (CRSsNP), T helper 1 polarization, interferon-gamma, transforming growth factor-beta levels often predominate [46, 47].

37.4.2.1 Omalizumab

Since Bachert showed local eosinophilic infiltration in 2001 [48] and Gevaert showed local IgE synthesis in tissue, it was hypothesized that omalizumab could be used in CRSwNP patients [49]. The first case report and case series about omalizumab were consisting of patients with asthma and concomitant CRSwNP who were receiving omalizumab treatment [50–52]. Some studies show the effectiveness and utility of omalizumab while others show the opposite. There are also studies showing the opposite. In a study, it was reported that the use of omalizumab in patients with asthma and concomitant chronic sinusitis (with/without polyp) had no superiority to a placebo [53]. On the other hand, in another study, allergic and non-allergic patients with nasal polyp and concomitant asthma were included. Patients received omalizumab treatment. As a result of the study in 16 weeks time, a decrease in endoscopic nasal polyp scores and nasal symptom scores and a significant increase in disease-related quality of life were observed [54]. Additionally, to effectiveness studies, Long et al. stated that there was no difference in the risk of malignancy compared to the placebo group at a 5-year follow-up of patients receiving omalizumab [55].

In the initial phase of omalizumab treatment, an increase in IgE is found paradoxically due to the formation of biologically inactivated IgE antibody complexes. The pharmacodynamic change in the serum reached detectable levels after 16 weeks of treatment, and a 50% decrease was observed in de novo IgE synthesis [56].

In conclusion, omalizumab is effective in improving or at least stabilizing the natural progress of CRSwNP in patients with concomitant refractory severe asthma. Omalizumab has been shown to be effective in allergic and non-allergic patients with CRSwNP and asthma. This is thought to be due to the role of local IgE in pathophysiology [54]. There is potential for allergy-independent benefit in asthma and CRSwNP patients [57]. Local IgE levels were found to be higher in patients with CRSwNP and asthma rather than in patients with CRSwNP without asthma [58]. Before planning treatment of the patients with CRSwNP without concomitant asthma, because of the high cost of treatment and the potential for the development of anaphylactic reaction, omalizumab treatment should be evaluated [54, 59, 60].

37.4.2.2 Reslizumab

Reslizumab, a humanized anti-IL5 antibody, acts by binding circulating IL5 to prevent its binding to receptors on eosinophils [57]. The first clinical study was conducted by Gevaert in 2006 for pharmacokinetic and safety information. In the study, subjects were given a single dose of reslizumab (3 mg/kg or 1 mg/kg), and blood systemic eosinophil and eosinophilic cationic protein (ECP) concentrations were monitored for 8 weeks. Single-dose reslizumab was well tolerated. There were no major adverse events. Patients were grouped according to total nasal polyp (NP) scores as responders and nonresponders to the treatment. Endoscopic polyp scores improved in only half of the cases. At the end of the study, IL5 concentrations were found to be high in the nasal secretions of patients who responded with reslizumab. The detection of IL5 concentration greater than the cutoff value>40 pg/mL in nasal lining secretion allows us to predict the response to treatment with reslizumab. In the same study, reslizumab treatment was found to be more effective in CRSwNP patients with asthma than in patients with asthma alone [61]. In this study, the subgroup that benefited most from anti-IL5 treatment were those CRSwNP patients with high levels of IL5 [62].

37.4.2.3 Mepolizumab

IL5 is one of the proinflammatory cytokines which regulates the activation, maturation, survival, and recruitment of eosinophils. IL5 can be synthesized from various cells such as eosinophils, mast cells, CD34+ progenitor T cells, T helper 2 cells, invariant natural killer cells, and group 2 innate lymphoid cells. Mepolizumab is a humanized anti-IL5 antibody. Unlike reslizumab, local IL5 concentrations in nasal lining secretion have no predictive effect on treatment with mepolizumab. Geveart et al. administered 750 mg mepolizumab iv, twice daily for 8 weeks. Nasal polyp scores, CT scores, and nasal peak inspiratory flow were evaluated after 8 weeks. (A dose of 100 mg SC was approved for eosinophilic asthma.) Most of the patients had decreased nasal polyp size. The dose of the drug was well tolerated [63].

Bachert et al. tested 750 mg mepolizumab on patients with severe CRPwNP who had surgical indications and were refractory to treatment (six times in 4 weeks with the addition of nasal steroid). At the end of 25 weeks, 30% of the patients did not need surgery. Despite the high dose, it was well tolerated. VAS scores, SNOT-22 test results, and endoscopic polyp scores improved [64].

37.4.2.4 Dupilumab

Dupilumab is a fully humanized antibody that binds alpha subunits of IL4 receptors. The IL4-alpha receptor is also recognized by IL13. Dupilumab modulates signaling through Th2 inflammatory pathway. In the study by Bachert et al., 16 weeks of topical nasal steroid (mometasone furoate) and dupilumab treatment were given to CRSwNP patients. The study findings revealed an effective reduction in endoscopic polyp scores, Lund-MacKayCT scores, and clinical symptoms [65, 66]. They found a significant reduction in serum IgE levels, serum thymus activation regulated chemokine (TARC) and plasma eotaxin3 levels. Targeting IL4 and IL13, which play a key role in the Th2 inflammatory pathway, may affect upper and lower airway pathological processes [67]. Dupilumab has FDA approval for asthma, atopic dermatitis, and CRSwNP in 2019 [68].

The addition of dupilumab to the daily standard intranasal steroid therapy has significantly reduced the need for systemic corticosteroids and surgery and has provided effective treatment for severe CRSwNP patients with comorbid asthma with few therapeutic options [69, 70].

37.5 Conclusion

The very high costs of biologic therapy and the fact that, unlike allergen immunotherapy, they do not alter the course of disease and require continued application mean that their use must necessarily be restricted. The degree of restriction will depend on several factors, one being the wealth of the society in which the patient is being treated and another the availability of other cheaper but effective treatments. In many countries, biologics should only be used for patients with life-threatening conditions, such as eosinophilic pauci-granulomatous arteritis (EGPA) where mepolizumab can decrease the need for oral corticosteroids [71] or uncontrollable severe asthma.

Real-world evidence of the effectiveness of biologics outside the rarified clinical trial population is needed, and the data should be amassed and analyzed.

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Recent Advances in Olfactory Dysfunction Treatment and Rehabilitation

38

Ali Bayram, Cemal Cingi, and Philippe Rombaux

38.1 Introduction

Olfaction is an important human sense, serving numerous functions in the routine daily life of human beings, such as monitoring the environment, warning of hazardous situations (e.g., fire, rotten food, natural gas leakage), in social functions and for satisfaction from foods with the contribution to taste and flavor. Olfaction starts with the transportation of odors through the nose and the perception of the odors begins in the olfactory epithelium. Patterns of these activations are then interpreted in the central nervous system. Any obstacle between the odorant molecules and the olfactory epithelium or any deterioration involving the neural processing and its central projections may cause olfactory dysfunction. This chapter focuses on the ongoing quest for optimal treatment of olfactory dysfunction and presents recent advances obtained from current treatment modalities.

38.2 Olfactory Dysfunction

Olfactory dysfunction is a pathological condition of a decrease or loss of smell that significantly impairs the patient's quality of life. The prevalence of functional anosmia is approximately 5% in the general population, whereas decreased olfactory ability was estimated to be as high as 15% with a significant contribution from

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_38

normal aging [1, 2]. The diagnosis of olfactory dysfunction can be made on the basis of a thorough interview with the patient and the use of psychophysical olfactory tests. Electrophysiological tests such as electroolfactogram (EOG), electroencephalogram, and olfactory event-related potential and imaging studies including computed tomography (CT) and magnetic resonance imaging (MRI) may provide additional information regarding the etiology and prognosis of the disorder. Functional imaging modalities (positron-emission tomography and functional MRI) detect cerebral blood flow alterations/changes in oxygenation of the blood in response to odorous stimuli and enable the mapping of brain activity changes in response to stimulation [3]. Olfactory dysfunction is typically classified according to the cause of olfactory loss (Table 38.1). The degree of olfactory dysfunction can also be categorized quantitatively (hyposmia, hyperosmia, anosmia) or qualitatively (parosmia and phantosmia) [2]. Olfactory dysfunction may have more than 200 causes (Table 38.2); however, the vast majority of cases occur due to sinonasal disease, and postinfectious and post-traumatic conditions.

Despite the fact that olfactory dysfunction does not get the attention it deserves from the medical community, an increasing number of diagnoses necessitates more focus on the underlying pathological mechanisms and new therapeutic strategies. The underlying etiological factor is the main predictor of the prognosis of olfactory

Table 38.1 Classification of olfactory dysfunction according to pathological location

Conductive	Blockage of airflow to the olfactory neuro-epithelium
Sensorineural	Impairment of olfactory neuro-epithelium or nerve
Central	Impairment of olfactory processing pathways

Table 38.2 Causes of olfactory dysfunction

Sinonasal disease	Toxins Smoking Work-related toxins (acids, benzene, cadmium)
Postinfectious	Drugs Local anesthetics (cocaine, procaine, tetracaine) Antimicrobials (streptomycin, macrolides) Anti-hypertensives (nifedipine) Anti-thyroid (propylthiouracil) Anti-depressant (amitriptyline) Chemotherapy Alpha-receptor antagonists
Post-traumatic	Congenital
Neurological disease Epilepsy Myasthenia gravis Stroke Parkinson's disease Alzheimer's disease	Other Neoplasms Septal surgery Endocrine disorders (Addison's disease, Turner's syndrome or hypothyroidism) Metabolic disorders (diabetes mellitus, hypertension) Migraine Radiotherapy

dysfunction. It is well-known that conductive olfactory dysfunction has a good prognosis after appropriate management compared to sensorineural and central types. Also, residual olfactory function, age, smoking, and parosmia are common factors related to prognosis. Treatment of olfactory dysfunction includes pharmacological therapy, surgery, and olfactory training (OT), whereas medical therapy is currently the most preferred treatment modality. Systemic and/or topical steroids play a pivotal role in the pharmacological treatment of olfactory dysfunction, especially caused by chronic rhinosinusitis. According to a previous European survey, 89% of clinicians prescribe topical intranasal steroids for olfactory dysfunction regardless of etiology [4]. With regard to the surgical treatment of olfactory dysfunction, endoscopic sinus surgery can provide a beneficial effect in chronic sinusitis with or without nasal polyposis, while the efficacy of surgical procedures for pathological conditions other than chronic rhinosinusitis still remains unclear [5, 6]. Researchers are still in search of a validated and effective remedy for long-lasting olfactory dysfunction with a preferable lack of side effects and low cost. Accordingly, there have been recent advances in the treatment of olfactory dysfunction, such as OT, phosphodiesterase inhibitors, and intranasal calcium buffers, with promising results.

38.3 Recent Advances in Treatment and Rehabilitation

38.3.1 Olfactory Training

In recent years, OT is suggested as an attractive therapeutic option for patients with olfactory dysfunction due to its safety, simplicity, and low cost, as shown in the literature [2]. The olfactory epithelium involves basal cell progenitors that have a neuro-regenerative capacity for the olfactory system, and the regeneration of epithelium has been shown to be promoted by repeated exposure to different odors [7, 8]. Although the exact mechanism has not yet been elucidated, OT aims to increase the regenerative capacity of olfactory neurons by performing a repetitive and structured smelling of odorants. In the classically administered protocol, patients are instructed to sniff one of four different odorants (flowery, fruity, spicy, resinous) twice a day over a long period of time.

Studies evaluating the efficacy of OT in the treatment of olfactory dysfunction have revealed promising results. In 2009, Hummel et al. performed a prospective, controlled study investigating the benefit of OT in patients with olfactory dysfunction [9]. The patients were instructed to expose themselves twice daily to four intense odors over a period of 12 weeks, and the olfactory improvement was evaluated by the Sniffin' Sticks test before and after the training. The study demonstrated that trained patients had significantly improved olfactory function in spite of different etiological factors including postinfectious, post-traumatic, or idiopathic. Accordingly, Konstantinidis et al. reported the benefit of OT in 72 patients with postinfectious and post-traumatic olfactory dysfunction [10]. Besides the patients with postinfectious and post-traumatic olfactory dysfunction, OT was also shown to

be an effective treatment modality in Parkinson's disease, in which olfactory dysfunction is an early characteristic of the disease [11]. In 2017, Sorokowska et al. reported a meta-analysis aimed to provide a quantitative estimate of the benefit of OT across three different olfactory abilities—smell identification, discrimination, and threshold for odor detection [12]. The meta-analysis demonstrated a positive and statistically significant effect of OT in the case of all olfactory abilities and concluded that OT should be considered an addition or alternative to existing smell treatment methods. Likewise, in the position paper written by Hummel et al., OT was recommended for patients with olfactory loss, although establishing the efficacy of the treatment necessitates a further evaluation of olfactory dysfunction caused by sinonasal disease [2].

Despite the existence of studies demonstrating the efficacy of OT, the optimal treatment protocol in terms of the exact therapy period and the characteristics of utilized odorants such as type, number, and concentration has not yet been fully clarified. The duration of the treatment protocol varied from 12 to 56 weeks according to the related studies. In 2014, Geissler et al. reported that a longer duration of training of 32 weeks seemed to increase the beneficial effect of the therapy in comparison to a 12-week treatment protocol [13]. Konstantinidis et al. compared the olfactory improvement after a long-term OT (56 weeks) versus a short-term Scheme (16 weeks) in patients with postinfectious olfactory dysfunction, and the long-term group had better results according to the Sniffin' Sticks test [14]. However, the authors also noted that a relatively sustainable improvement remained even at 56 weeks in the short-term training group. Altundağ et al. reported that OT should last at least 24 weeks in order to get satisfactory results, while they also showed improved results by adding more odors to the training protocol [15]. In a randomized, controlled, multicenter study, Damm et al. demonstrated that OT with higher concentrations was beneficial to improvement in patients with persistent postinfectious olfactory dysfunction [16]. The authors also stated that OT was useful particularly in patients who initiated the therapy within 12 months after the beginning of the dysfunction. In a recent study, Oleszkiewicz et al. investigated the optimal protocol for OT with particular focus on quantity and quality of odors utilized and reported that the outcomes of OT are not strongly influenced by the training regimen [17].

The source of olfactory improvement after OT with regard to peripheral or central origin has remained uncertain to date. According to the functional MRI findings, OT altered the chemosensory processing networks in patients with olfactory dysfunction. Kollndorfer et al. [18] demonstrated a neural plasticity effect of OT by inducing neural reorganization processes in functional MRI. Accordingly, in the following study of Kollndorfer et al. [19], the authors showed an increase in functional connectivity for the olfactory network (caudate nucleus), the integrative network (insular cortex), and the somatosensory network (supramarginal gyrus) in patients with postinfectious anosmia after OT. The alterations induced by OT were also evaluated with psychophysical tests and functional MRI examinations concurrently [20]. Pellegrino et al. investigated the smelling improvement

via Sniffin' Sticks tests in anosmic ($n = 23$) and hyposmic ($n = 14$) patients caused by trauma after OT. Additionally, functional MRI examinations were performed before and after OT in order to identify functional network and olfactory bulb alterations. In this study, hyposmic patients had better odor recognition with increased ipsilateral activations in semantic processing areas including the left angular gyrus, Broca's area, and the left superior frontal gyrus in functional MRI after training. Also, anosmic patients demonstrated improved olfactory thresholds to 2-phenylethanol with activation in the right superior frontal gyrus, whereas none in the patient group showed olfactory bulb volume alterations. Al Aïn et al. [21] investigated the effects of a 6-week intensive olfactory study on olfactory function and brain neuroplasticity with a series of olfactory tests and functional MRI in a well-controlled study and reported improved olfactory function in the OT group compared to the control group. In addition, training patients had increased cortical thickness in the right inferior frontal gyrus, the bilateral fusiform gyrus, and the right entorhinal cortex in functional MRI, and the authors concluded that intensive OT could improve olfactory function with changes in the structure of olfactory processing areas of the brain. Although the majority of the relevant studies suggested training-induced improvement was central rather than peripheral in olfactory dysfunction, studies demonstrating the role of stimulus-induced plasticity at the level of the olfactory epithelium also exist in the literature [22, 23]. In a recent study, Hummel et al. measured electrophysiological EOG responses to a pleasant, rose-like odor and to an unpleasant odor (rotten eggs) in patients with olfactory dysfunction before and after OT and compared the results with healthy controls [23]. The results of the study showed that OT is related to an increase in EOG responses, implicating stimulus-induced plasticity starting at the level of the olfactory epithelium. Therefore, the authors concluded that OT may affect olfactory processing not only at the central level but also at the level of the olfactory epithelium.

The olfactory processing system has close connections with trigeminal systems. During olfaction, the olfactory system is employed for odor quality perception, while the trigeminal system aids transmitting sensations such as pain, temperature, or burning [24]. Functional imaging studies have demonstrated a relationship between olfactory and trigeminal systems on a cerebral level, since trigeminal stimulation activates pain processing areas, including the primary somatosensory cortex, the insula, or the anterior cingulate cortex, as well as olfactory-related areas, such as the orbitofrontal cortex [25, 26]. Kollndorfer et al. reported that a functional trigeminal system still existed in patients with olfactory dysfunction and assumed that a functional trigeminal pathway may trigger the recovery of olfactory function, which was observed after OT treatment [19].

In conclusion, although the benefit of OT has been shown in the treatment of olfactory dysfunction, future work is required to determine the underlying mechanisms of the benefit, which may help to assess the optimal training regimen, particularly with regard to duration and frequency of therapy, and the content of the utilized odorants.

38.3.2 Phosphodiesterase Inhibitors

When odorant molecules reach the olfactory epithelium, a series of molecular events are triggered in order to transform the chemical energy into a neural signal. Odorant stimulation of olfactory receptor neurons mediates intracellular activation of type III adenylate cyclase by means of G protein, which leads to intracellular accumulation of cyclic adenosine monophosphate (cAMP). Increased intracellular cAMP induces calcium influx and thereby neuron depolarization. In the olfactory epithelium, cAMP is metabolized by a calcium/calmodulin-dependent phosphodiesterase (PDE) [27]. The theoretical consideration for utilizing phosphodiesterase inhibitors (pentoxifylline, theophylline) in the treatment of olfactory dysfunction is based on increasing intracellular cAMP concentration by means of calcium/calmodulin-dependent phosphodiesterase inhibition.

Gudziol and Hummel published the first article investigating the effect of pentoxifylline on olfactory function and found an increased olfactory sensitivity after pentoxifylline administration [28]. Henkin et al. evaluated the efficacy of theophylline in 312 hyposmic patients and reported that oral theophylline was beneficial in improving olfactory dysfunction [29]. In a study conducted on 19 patients with congenital hyposmia, smell function was initiated in 63% of the study population after oral theophylline treatment [30]. However, the required oral theophylline dose in order to provide adequate intranasal mucus cAMP levels poses a risk of inducing adverse effects such as gastrointestinal tract discomfort, restlessness, sleep difficulties, and tachycardia. For that reason, oral theophylline treatment necessitates regular blood theophylline level measurements for determining adequate drug absorption and lack of toxic effects [31]. Accordingly, researchers aimed to evaluate the efficacy of intranasal administration to overcome the disadvantages of oral theophylline treatment. In an experimental study, topically administered theophylline was shown to enter the olfactory epithelium of supravital mice and have an effect on olfactory signal transduction by means of inducing a decrease of the EOG amplitude by up to 25% [32]. Henkin et al. [31] demonstrated that intranasal theophylline treatment is safer and more effective than oral theophylline in improving hyposmia and hypogeusia. Nevertheless, contrary to the abovementioned studies addressing the benefit of phosphodiesterase inhibitors in the treatment of olfactory dysfunction, in a recent pilot study, Whitcroft et al. showed that a short-course of oral pentoxifylline did not seem to be effective in post-traumatic olfactory dysfunction [33]. Therefore, administering phosphodiesterase inhibitors for the management of olfactory dysfunction still requires further data obtained from randomized, controlled clinical trials.

38.3.3 Intranasal Calcium Buffers

During olfactory transduction, increased intracellular cAMP induces the opening of cyclic nucleotide-gated (CNG) channels at the surface membrane of olfactory receptor neurons, and the presence of cation influx through CNG channels causes

axonal firing. The negative feedback role of calcium during the olfactory process has been identified in recent studies since calcium reduces the sensitivity of CNG channels to cAMP [34]. Accordingly, a rise in mucosal calcium induces negative feedback and is suggested to play a role in the adaptation of the olfactory response to prolonged stimulus exposure. In the treatment of hyposmia, intranasal sodium citrate is administered as a calcium sequestrant to decrease mucus free calcium, hence theoretically considered to reduce the negative feedback and improve olfaction [35].

Panagiotopoulos et al. [35] administered a sodium citrate buffer solution to the nasal cleft of 31 patients with olfactory dysfunction and reported improved odor function in the majority of cases. Whitcroft et al. designed a prospective, single-blind, and placebo-controlled trial investigating the efficacy of intranasal sodium citrate in patients with postinfectious olfactory dysfunction. The authors studied olfactory function (odor threshold and identification) using the Sniffin' Sticks test before and after treatment and found a statistically significant olfactory improvement following sodium citrate treatment [36]. Also, in a randomized controlled trial, sodium citrate spray was found to enhance olfaction when compared with sterile water in 55 patients with non-conductive olfactory impairment [37]. However, studies investigating intranasal sodium citrate treatment in olfactory dysfunction are still limited in the literature, and further work is required to determine the clinical utility of such treatment.

38.3.4 Other Treatment Options

Traditional Chinese acupuncture is one of the oldest therapeutic modalities and has been performed for thousands of years. Acupuncture therapy was suggested for olfactory treatment due to its modulatory effect upon the microcirculation. In 2010, Vent et al. evaluated the benefit of 30-min acupuncture sessions for 10 weeks in 15 patients with post-viral olfactory dysfunction and compared the olfactory improvement within a similar patient group who had been treated with vitamin B complex for 12 weeks via the Sniffin' Sticks test [38]. The author found that the efficacy of acupuncture was significantly better than vitamin B treatment and offered acupuncture treatment as a new therapeutic regimen for post-viral olfactory dysfunction. Dai et al. investigated the impact of acupuncture in patients with post-viral olfactory dysfunction who did not respond to steroid and vitamin B therapy [39]. The authors reported that acupuncture significantly improved olfactory function and may have benefit in the treatment of post-viral olfactory dysfunction that is refractory to drug therapy. However, there is still limited data derived from placebo-controlled studies with larger samples in the literature regarding the benefit of acupuncture in the treatment of olfactory dysfunction.

Minocycline, a member of the tetracycline class of antibiotics, has been used in Huntington's disease and various other neurological disorders due to its anti-inflammatory and neuroprotective properties. An animal study showed that minocycline delayed the death of olfactory neurons and minocycline was suggested as a

treatment option for olfactory dysfunction [40]. Siopi et al. reported minocycline as a promising pharmaceutical agent in olfactory bulb lesions caused by traumatic brain injury [41]. However, although minocycline was suggested as a promising target in animal studies, Reden et al. showed no significant benefit in the treatment of 55 patients with postinfectious olfactory dysfunction in a randomized, prospective, double-blind, and placebo-controlled study [42].

Retinoic acid, a vitamin A metabolite, is normally present in the olfactory epithelium and has a critical role in the regeneration of olfactory receptor neurons. However, the effect of vitamin A supplementation in the treatment of olfactory dysfunction revealed varying results. Reden et al. [43] evaluated the effect of vitamin A treatment at a dose of 10,000 IU per day for 3 months in a group with postinfectious and post-traumatic olfactory dysfunction; however, vitamin A did not provide any significant improvement over placebo. Kartal et al. [44] found that systemic isotretinoin (a synthetic analog of vitamin A) administration improved the sense of smell. In a recent study, Hummel et al. [45] reported that combined therapy including intranasal vitamin A and OT may be of benefit in the treatment of postinfectious olfactory loss and recommended further prospective, placebo-controlled studies in order to confirm the utility of intranasal treatment in olfactory dysfunction.

38.4 Conclusion

Olfactory dysfunction represents one of the most challenging pathological conditions for patients and clinicians in otolaryngological practice. To date, there is no validated pharmacotherapy specifically utilized for olfactory dysfunction caused by etiological factors other than chronic rhinosinusitis with or without nasal polyposis. However, among the recent therapeutic options, OT seems to provide promising results for postinfectious and post-traumatic olfactory dysfunction, although future larger randomized controlled studies are required to clarify an accurate training protocol.

Acknowledgement We would like to thank Dr. Thomas Hummel for his valuable contributions.

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Does Nasal Disease Cause Headaches?

39

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39.1 Introduction

It is uncommon for a headache that is due to rhinosinusitis (aka "sinus headache") to occur. In such a situation, an initial sinus infection by a viral or bacterial pathogen leads to formation of a viscous, discoloured discharge from the nose, hyposmia or anosmia, pain or a sense of pressure in the facial region and usually pyrexia. Pain in the face and headache normally abate within a week of the infection resolving. Ongoing pain should prompt a review of the diagnosis [1].

The International Classification of Headache Disorders has published useful criteria which may be used to distinguish different kinds of headache. In sinus headache, pain over the face, facial pressure, blockage of the nose and sinuses are present. Additionally, the following symptoms, which are also present in migraine disorders, may occur: nausea, photosensitivity or noise intolerance, moderate to severe headache, a pulsatile or throbbing sensation and exacerbation due to activity [1].

Despite the popularity of the term "sinus headache" among patients themselves and general practitioners, in the media and in advertising copy, its use is deprecated by ENT specialists, allergists and neurologists, who feel that the term lacks precision and may lead to inappropriate interventions [2]. The term sinus headache is generally applied when a headache is accompanied by pain in the face or facial

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_39

pressure. It is the facial pain and pressure that brings the association with sinus disease. A more precise term to use is "rhinogenic" headache, provided the physician has reasonable grounds to consider that the symptoms arise from a nasal problem, but, given the established usage of the term "sinus headache" by both general practitioners and sufferers, this is the terminology employed by rhinology and neurology specialists when recruiting patients into clinical trials investigating the condition. The Rhinosinusitis Task Force (RTF) of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) produced criteria to use when diagnosing acute and chronic sinusitis [3, 4]. It is noteworthy that pain in the face or pressure on the face no longer count as being sufficient for the diagnosis of chronic sinusitis, although these symptoms may be considered alongside the cardinal diagnostic criteria [5].

39.2 Classification of Headache Disorders Attributed to the Nose or Paranasal Sinuses

According to the ICHD-3 beta version, two categories of headache exist which may be considered to originate from nasal or paranasal sinus pathology:

1. Headache secondary to acute rhinosinusitis
2. Headache secondary to chronic or persistent rhinosinusitis [6, 7]

39.3 Sinogenic Facial Pain and Headache

Individuals who have pain in the face from acute sinusitis also have other symptoms such as a blocked nose, reduced ability to smell or a pus-filled discharge from the nose. On endoscopy, pus, swelling and inflammation are apparent [8, 9].

There is no correlation between how severe pain is reported in sinusitis and how significant it appears radiologically [10].

In a study by Jones et al., 679 cases of apparent sinusitis were examined. In just 18% (119 individuals) was pain the presenting complaint, and of these 18%, sinusitis was not confirmed on either endoscopy or CT in a quarter of cases [11].

Acute sinusitis is treated with antibiotic therapy, decongestants (local or systemic), pain killers and proactive fluid management. If symptoms are not severe (temperature < 38 °C, pain mild to moderate), then intranasal corticosteroids are superior to antibiotics [12]. Typical antimicrobials in use are amoxicillin or one of the macrolides with a course lasting anywhere from 10 to 14 days. In cases where the condition is refractory to treatment, sinusitis is ongoing when the first course finishes or sinusitis is acute-on-chronic, recourse may be second-line antimicrobial therapy, e.g. co-amoxiclav, second- and third-generation cephalosporins and clindamycin [13].

If pharmacological treatment is insufficient, consideration needs to be given to endoscopic sinus surgery (ESS). Between 56 and 77% of those who undergo ESS

report a lessening of pain over the face and lower facial pressure. According to some research, pain over the face was also lessened following ESS in cases of headache not attributed to sinusal pathology. Nonetheless, facial pain does return in the majority of cases within 9 months [13, 14].

According to the criteria issued by the International Headache Society (IHS), a sinus headache consists of the following [15]:

1. Headache occurring in the frontal region, with pain in at least one of the following: face, ears and teeth. Criteria C and D must be met.
2. Either acute or acute-on-chronic rhinosinusitis are present, as observed either clinically, on nasal endoscopy or on imaging (CT+/− MRI), or by laboratory testing.
3. The timing of headache or pain over the facial region coincides temporally with the beginning of rhinosinusitis or the start of an exacerbation.
4. Headache or pain over the facial region, or both, that ends less than a week after sinusitis (acute or acute-on-chronic) resolves either spontaneously or with therapy.

In most cases, pain from the nose and sinuses is felt elsewhere (referred). Its character is a deep ache with little fluctuation. Location of pain is a guide to the most likely involved sinus(es). The following are the usual referral patterns for pain [16]:

- Pain in the forehead, over the vertex and behind the eyes is referred from the frontal sinus.
- Pain in the cheek and in the maxillary teeth is from the maxillary sinus.
- Pain in the nasion, behind the eyes and in the temples is from the ethmoid sinus.
- Pain over the vertex, at the back of the head, over the forehead and behind the eyes is from the sphenoid sinus.

39.3.1 Rhinosinusitis

In 2015, the American Academy of Otolaryngology–Head and Neck Surgery Foundation updated the guidance issued on the management of rhinosinusitis in adults, with a powerful recommendation that acute rhinosinusitis due to bacteria be distinguished from acute rhinosinusitis secondary to upper respiratory infection by viruses or from causes not related to infection. They point out the necessity for gathering objective evidence of infection in the nose and sinuses. The following are further recommendations [17]:

- In an adult case of acute rhinosinusitis without complications, the case may be managed either by waiting to observe any need for antimicrobial therapy or by prescribing a first trial of antibiotic.

- Where an initial trial is chosen, a course of amoxicillin or co-amoxiclav for 5–10 days is suitable.
- Review the case and check the diagnosis, being alert to other possible causes. Where the rhinosinusitis deteriorates within 1 week after diagnosis or is not resolving, it may be considered to be complicated rhinosinusitis.
- It is valuable to differentiate between chronic rhinosinusitis (CRS) or recurring episodes of acute rhinosinusitis on the one hand and separate acute bacterial rhinosinusitis episodes or other pathologies affecting the nose and sinuses, on the other hand.
- In cases of persistent rhinosinusitis or repeated acute rhinosinusitis episodes, investigate for possible predisposing conditions, e.g. asthma, CF (cystic fibrosis), immunodeficiencies and disorders of ciliary motility.
- For cases of CRS, note whether polyposis is also present.
- In CRS, either irrigating the nose with saline or locally applied glucocorticoids, or indeed both treatments, is suggested to relieve CRS symptoms.

39.3.1.1 Sinus Symptoms

Despite its popularity as a diagnosis by physicians and a self-diagnosis by patients, seemingly sinusitis (whether acute or chronic) rarely produces a recurring headache [18–20].

A headache arising from pathology in the nose or sinuses is not typically diagnosed on radiological grounds, as nasal endoscopy usually suffices to make the diagnosis. However, if there are concerns that sinus pathology has extended intracranially, both non-contrast and contrast-enhancing MR imaging of the head is required [21].

The autonomic division of the trigeminal nerve is typically involved in cluster headaches and often also in migraines, producing the symptoms of nasal stuffiness, nasal discharge, tearing and alterations in colour and temperature together with pupillary size [22].

Because sinus-related symptoms occur with high frequency, clinicians may often be misled into diagnosing migraine or, more rarely, a tension-type headache as a "sinus headache". A study with observational design investigated 2991 individuals with a putative diagnosis of sinus headache (either diagnosed by a doctor or by the patients themselves). Eighty-eight percent of the cohort were found to have a headache matching the criteria for migraine or migrainous headache, while 8% matched the criteria for tension-type headache [22]. Upon review, in those cases where migraine or migrainous headache was the diagnosis, facial pressure and stuffiness were frequent symptoms alongside more classical migraine symptoms such as pulsatile headache and oversensitivity to activity, noise and bright light [22].

There are certain characteristics of pain that is solely due to sinus disorders, and these help to differentiate this type of pain from that occurring in migraine [2, 23]. Pain in sinus disorders is frequently said to resemble pressure or to be dull in quality. This pain described occurs on both sides of the face and is localised around the eyes. Nonetheless, in patients who are diagnosed with a deviated nasal septum, middle or inferior conchae hypertrophy or unilateral sinuses involvement, pain may

be limited to one side only. Pain of sinusal origin usually occurs in conjunction with blockage of the nose or stuffiness, has a duration of several days and has no association with nausea, vomiting, sensitivity to light or sensitivity to noise [21].

Imaging-based evaluation of the degree and site of sinus disease has no correlation with patient reports on how severe pain is, where it comes from and how large an area is affected [23].

Generally speaking, severity and location of pain are the characteristics expected in headaches associated with rhinosinusitis [2, 24, 25]:

- Headaches that follow the same format repeatedly and prevent activities of daily living are probably migraines.
- Repeatedly occurring headaches that give nose-related symptoms and spontaneously resolve are also probably migraines.
- If nose-related symptoms are very marked and headache is just one such symptom, it is important to exclude an underlying ENT condition.
- Where a headache occurs in conjunction with pyrexia and discharge of pus from the nose, a rhinogenic cause is most probable.

39.3.1.2 Chronic Rhinosinusitis and Headache

The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) defines CRS as a condition lasting a minimum of 12 weeks and characterised by at least two of the following: discharge of mucus and pus, blocked nose, pain or pressure or sensation of fullness in the face, hyposmia and evidence for an inflammatory response. On endoscopy there should be pus formation, swollen mucosa or polyposis. Imaging should reveal inflammation within the paranasal sinuses [26]. The characteristics recognised by the IHS in identifying a headache as rhinogenic being or sinogenic have been increased in the light of recent evidence. The International Classification of Headache 3, beta version [7, 27, 28], now recognises CRS as a non-primary reason for headaches to occur. CRS in fact puts up the risk of persistent headaches by nine times [27]. In a review of headaches due to CRS after 3 years, the following were found to promote recovery: operations on the nose, intranasal steroids, stopping headache treatments that were being overused, stopping decongestant therapy or for unknown reasons [27].

39.4 The Relationship Between the Nasal Sinuses and Migraines

The principal anatomical structures that are implicated in migraine are the vessels supplying the meninges, the trigeminal nerve, the caudal nucleus of cranial nerve V, the thalamus, the hypothalamus and certain other regions in the brainstem. Stimulation of any of these regions, if it reaches the threshold, may provoke migraine symptoms. These regions are linked in such a way that a positive feedback loop is set up. Individuals who regularly have migraines, it has been discovered, respond in an exaggerated fashion to sensory stimuli. This phenomenon is termed

hyperexcitability. Pain perception from the sinuses passes along the trigeminal nerve. The anterior ethmoidal nerve arises from the ophthalmic division of cranial nerve V (V1), which supplies pain perception to the anterior conchae. There are pain fibres within the maxillary division of cranial nerve V (V2) that pass via the sphenopalatine ganglion (SPG) to the oral roof in the form of the palatine nerves and to the conchae and rear portion of the nasopharynx in the form of the nasopalatine nerves. The second trigeminal division also gives rise to the infraorbital nerve, which innervates the front of the nose and the external bridge of the nose. The SPG (sphenopalatine ganglion) mediates the way sinus symptoms and migraines interact [29].

The SPG mainly contains parasympathetic elements that are within the maxillary division of cranial nerve V. The nasopalatine nerve conveys nociception from the roof of the oral cavity, and the nasopalatine nerve does the same for the conchae and rear portion of the nasopharynx. These both synapse in the SPG. The SPG approximates the middle meningeal nerve, which supplies pain sensation to the dura of the middle cranial fossa and a portion of the periorbital region. The SPG also contains elements from the two divisions of the autonomic nervous system. The parasympathetic elements arise from the superior salivatory nucleus of the pons and modulate trigeminal impulses [6, 30]. Parasympathetic fibres run in parallel to the facial nerve and synapse in the SPG via the geniculate ganglion [31].

From the foregoing description of the complicated neuroanatomical layout within the sinuses and surrounding structures, it may be predicted that migraine, which involves hyperexcitability of cranial nerve V, may lead to activation of both the pain-sensing fibres within the nose and sinuses and autonomic arousal within the trigeminal nerve and associated nuclei. This hyperexcitability of the trigeminal leads to facial pain, including the area over maxillary regions, and tearing. Other signs include red eyes, fullness in the face and swelling around the eyes. Infection within the sinus or anatomical problems may provoke sinusitis, which causes activation of the trigeminovascular complex. The trigeminovascular complex affects the nervous activity of the trigeminal nerve and also affects the meninges, which can give a headache and potentially set off migraine-type symptoms, such as sensitivity to light/noise and nausea, with or without vomiting. This may be particularly so in patients already predisposed to developing migraines [32, 33].

39.5 Sinus Mucocoeles

Sinus mucocoeles, also termed mucus-retention cysts, are chronic, gradually expanding, lesions that produce cysts. If a mucocoele attains sufficient size, it may press up against the bone that forms the boundaries of the sinusal space. A maxillary mucocoele may block the ostial meatus and thus induce sinusitis. The most important type of mucocoele in clinical practice is a frontoethmoidal mucocoele, as it may be responsible for a frontal headache and eye pain. Mucocoeles of sphenoethmoidal type may produce pain at the back of the skull, the top of the head or deep inside the nose. Mucocoeles are treated by endoscopy, operative excision or marsupialisation [3–36].

39.6 Contact Points

Another potential cause of pain involving a nasal problem is contact points in the mucosa. The way to diagnose pain caused by a contact point is to see if inducing vasoconstriction at the point where the mucosae come into contact makes the pain go away [37]. There is some debate about mucosal contact points as a cause of facial pain. Some researchers have found that these exist in the same numbers in both those with facial pain and those without [38]. In contrast to such findings, however, it has been demonstrated by other researchers that operations undertaken to remediate mucosal contact points lead to less facial pain [39].

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40 Upper and Lower Airways Interaction: Is the United Airway Disease Concept a Reflection of Reality? How Important Is It?

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40.1 Introduction

Atopy can manifest as allergic asthma or allergic rhinitis (AR), and both disorders frequently co-occur. AR in childhood is known to strongly predispose individuals to developing asthma in adulthood. The allergic airway syndrome has both inherited and environmental contributions. A clearer understanding of the risk factors that underpin atopic airway disease and how the parts of the airway interact is a necessary step towards a more rational approach to treatment. Researchers have hypothesised a number of different ways in which the upper and lower airways may influence each other in AR and asthma. That nasal pathophysiology has effects on the lower airways in asthmatics has been repeatedly shown to be true. Explaining this interaction as due to individuals aspirating the contents of the nose or as due to nervous system reflexes runs into the problem that supporting evidence cannot be found. Indeed, the bulk of the evidence until now supports the idea of the upper and lower airway as a single pathophysiological system, linked by both circulating factors and the bone marrow. Circulating interleukin-5 levels and eosinophil numbers are raised, and adhesive function enhanced following localised interaction with an antigen [1].

For individuals in whom asthma and rhinitis co-occur, the disorder is typically of greater severity and it costs more to treat. The unified airway model is significant in considering how best to treat, prevent and manage asthma and rhinitis [2, 3]. Since

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_40

it is common for allergic rhinitis to occur in association with asthma or to occur before asthma develops, the Allergic Rhinitis and Its Impact on Asthma (ARIA) organisation, with the backing of the WHO, advocates seeing AR as predicting the risk of asthma and examining for bronchial disease in any patient who presents with AR [4, 5].

The mucosal lining of the nose has many features in common with that lining the bronchi. A key concept connecting these mucosae is that of functional complementarity, which suggests the nose offers protection to the lungs [6], which goes beyond simply conditioning the air before it eventually enters the lungs [7].

Both in terms of morphology and function, then, the upper and lower portions of the airway can be conceptualised as a unified whole. Evidence has been accruing for many years in the form of observations made in both healthy and diseased individuals [8, 9].

40.2 Epidemiology

Above 80% of allergic asthma sufferers also have rhinitis, of which some 76% had symptoms of rhinitis prior to the development of asthma [10]. Allergic rhinitis lasted longer [11] and had greater severity [12] in patients with bronchial hyperresponsiveness (BHR). In addition, comparison of AR cases with healthy controls revealed a threefold increase in the risk of developing asthma [13–15]. It is currently accepted that AR occurs prior to asthma in the majority of cases and that severity of AR predicts deterioration in asthma [1].

A number of epidemiological studies have looked into the relationship of asthma and AR, and it has been demonstrated repeatedly that the two conditions are overlapping [16]. Asthma exists in around 19–38% of sufferers from AR, whilst AR is found in between 30 and 80% of patients with asthma. However, these numbers are likely to underrepresent the true incidence, since newer research has given a frequency for AR of 98.9% in sufferers from allergic asthma and 78.4% if the asthma is not allergic in type [17]. Furthermore, even where AR exists without asthma, BHR is commonly observed [18]. Indeed, methacholine or histamine could provoke BHR is around 30% of such cases [6, 7, 9, 19].

Thus, if we accept that rhinitis is present in more than 80% of asthma patients and that asthma exists in 10–40% of rhinitis patients, there are grounds to believe in the idea of “one airway, one disease”.

AR is accepted as a risk factor in the development of asthma [6], in other words suffering from prior episodes of breathing difficulties, e.g. wheezing, being short of breath, having a tight chest and coughing, accompanied by restriction on expiratory flow rates of a variable kind [7, 18]. Individuals with a nonallergic type of AR (NAR) are also more likely to get asthma of a nonallergic type. NAR itself features a later onset than AR and encompasses a disparate group of related disorders [7, 20].

40.3 Pathophysiology

The upper airway is where allergens and physical or chemical irritants first come into contact with the body. If the allergic response they provoke is no more than mild, it is possible that the lower airway will not be affected [7, 21].

The normal physiological functions of the nose encompass conditioning of breathed-in air, catching tiny particles in this air, smelling and components of immune defence, e.g. sternutation, mucociliary activity and production of immune system signalling molecules [22]. The nasal physiology is disturbed in AR, and this then creates issues with lower airway function, too [1]. It was shown that nasal hair providing a nose filtration function to allergenic pollens has a protective effect on the risk of developing asthma in seasonal allergic rhinitis patients [23]. On the other hand, there is also interaction between the eye and the nose, and the conjunctiva may be considered as a part of the one airway concept [24].

There is continuity between the upper and lower portions of the respiratory tree, including many similarities at the macroscopic and microscopic anatomical level, arising from the common purpose of delivering air into and out of the lungs [9]. The nasal mucosae overlie bone and are richly vascularised, whilst the mucosae of the bronchi are surrounded by smooth muscle [7, 25]. Allergic disease of the airways is provoked when aeroallergens are inhaled and stimulate mast cells or basophils, which carry surface-located IgE immunoglobulins, resulting in a hypersensitivity reaction. These IgE receptors have specificity for a particular epitope. IgE then cross-links, triggering degranulation of histamine and tryptase, as well as the release of immune molecules synthesised from membrane lipid precursor molecules (the leukotrienes) and cytokines [26, 27].

The immune system responds once an antigen-presenting cell interacts with an allergen by means of the membrane-mounted IgE receptor. T-helper (T_H) cells become active when they "see" antigenic fragments presented by MHC (major histocompatibility complex) class II molecules. T_H2 cells specific to the particular allergen synthesise IL-4 and IL-13 alongside CD154, and this initiates the IgE class-switching process [7, 28, 29].

The most probable pathogenetic mechanism that accounts for the combined response from both proximal and distal portions of the airway is that an immune response confined initially to one location turns into a systemic reaction through activation of cells within the bone marrow, which then migrate to various points in the respiratory tree. Additionally, pro-inflammatory molecules may reach the distal airways by postnasal drip or via the bloodstream [28]. Even if asthma is not present, atopic individuals or those with AR have lower airways in which the mucosal basement membranes are thickened, a sign of the remodelling that typically occurs in the lower airways in asthma. This helps to confirm the hypothesis of a unified airway response [27, 30].

When an antigen with multiple epitopes is encountered by IgE, the Fc$\sum$R1 molecule is activated, leading to an immediate-type hypersensitivity response. This response is key to how AR and allergic asthma occur [28]. In the immediate

response, both stored chemical signals and rapidly produced signals are excreted, causing redness, swelling and pruritus of the skin, sternutation and nasal discharge from the upper portion of the airway, whilst coughing, spasm of the bronchi, swelling and mucus formation indicate involvement of the lower portion of the respiratory tree [28].

There may be a number of ways in which the airway is induced to react. One such is the nasobronchial reflex arc, which consists of an afferent portion, the nasal sensory fibres of the fifth cranial nerve, and an efferent portion consisting of the tenth cranial nerve innervating smooth muscle of the airways to produce a contractile response. Its significance has long been discussed [7, 21].

Infectious rhinitis, rhinosinusitis, bronchiolitis and pneumonia may all result from bacterial or viral infections. Infections may also lead to worsening of COPD (chronic obstructive pulmonary disease) or asthma [31]. The respiratory epithelium may be harmed through exposure to tobacco smoking or air pollution in general as well as polluted air related to an occupation. This injury may provoke chronic inflammation, resulting in chronic bronchitis, or may initiate neoplastic change (beginning with metaplasia) in both proximal and distal portions of the airway. Not only is smoking the key risk factor for COPD and malignant neoplasia of the larynx and bronchi, but it is also the key risk factor in rhinitis [32, 33].

Research conducted using both asthma cases and healthy controls has shown that inhaling cold, dry air via the nose leads to greater resistance to airflow in the distal parts of the respiratory tree [34, 35]. Another key study indicated that airway hyperresponsiveness went up after allergen challenge in the nose, in a group of patients with asthma who gave a history of deteriorating symptoms of asthma at the time of seasonal flare-ups in AR [36].

40.4 Risk Factors

The familial nature of atopy has been well established, and genetics plays a role in establishing an atopic diathesis. The hereditability of asthma is between 35 and 95%, whilst for AR the corresponding figure is between 33 and 91% [37]. Of late, Liu et al. [38] have hypothesised that the TNFSF4 and FAM167A-BLK genes contain single nucleotide polymorphisms implicated in both asthma and AR, whilst Zhao et al. [25, 37] found that the PBX2 gene in the 6p21.3 asthma susceptibility locus correlated with greater likelihood of developing AR and asthma. Epigenetic modifications in utero (due to diet; nutrient consumption, in particular, vitamin D [39, 40]; toxic exposure to tobacco; polluted air; microbial infections) influence how genetic susceptibility develops and can alter organogenesis and immune functioning, either directly or indirectly [25, 41].

AR and asthma share the feature that hyperreactivity is mostly to allergens that occur widely, namely, airborne allergens [25, 42].

Nasal blockage in AR generally means that sufferers tend to prefer to breathe through their mouths, but this unfortunately reduces the ability of the nose conditioning the air and filtering out noxious particles. In an individual with an

appropriate diathesis, inflammation may develop, as may BHR [43]. Asthma sufferers may find that inhaling cold air induces a bronchoconstrictive response. Nasal breathing of cold air does not affect FEV1, but inhalation via the mouth causes a noticeable deterioration in FEV1 [44].

In cases where secretions from the nose have been swallowed or aspirated, traces can be found along the entire length of the gut. Coughing secondary to postnasal drip is probably mediated through activation of receptors in the pharynx and larynx [45]. Aspirating nasal contents can be concerning in individuals whose level of consciousness is lowered and where coughing is suppressed, such as in patients receiving artificial ventilation [46]. It appears, however, that aspiration does not participate in the interactions between the nose and the bronchi in non-diseased states [47].

It already seemed that absorption from inhaled air into the bloodstream occurred to a greater extent across the mucosae of the bronchi than that of the nose, most likely because the surface area within the lung exceeds the surface area of the nose and because blood vessels are in closer proximity. It has now become more evident that nasobronchial interaction is also humorally mediated. When cases of AR were compared with controls following challenge to the nose and bronchi, interleukin-5 titres were raised, as were eosinophil counts [48, 49]. Eosinophilic recruitment to the airway mediated through IL-5 has been demonstrated by Wang et al. [50] IL-5 is also of central importance in bone marrow production of eosinophils. Saito et al. evaluated the mucosa of the nose and the bone marrow for signs of inflammation in experimentally induced rhinitis, where allergenic provocation of the nasal mucosa was performed. They found raised levels of eosinophilic precursor cells [51].

40.5 The Link Between Allergic Rhinitis and Asthma

There are similarities between the form inflammation takes in AR and asthma, which both feature a proliferation of eosinophils and T-lymphocytes. The histopathological appearances of the nose closely resemble those of the bronchial airways, an observation that was made even as far back as the late 1800s, by the German pathologist Weber [52].

Sneezing, nasal discharge and nasal blockage are classically associated with AR, but other problems can and do occur: lower life quality, possible sleep disorder, affective issues and reduced participation in activities and socialisation [53–55]. Asthma, on the other hand, refers by definition to a disorder in which the airways are temporarily obstructed and thus depends for its diagnosis on demonstrating abnormal pulmonary function and hyperresponsiveness of the bronchi. Asthmatic individuals typically experience dry cough, wheeze when breathing out, a tight chest and shortness of breath, these symptoms being provoked by exposure to allergenic or irritant substances and infective agents [56].

Asthma exists in around 19–38% of sufferers from AR, whilst AR is found in between 30 and 80% of patients with asthma. However, these numbers are likely to underrepresent the true incidence, since newer research has given a frequency for AR of 98.9% in sufferers from allergic asthma and 78.4% if the asthma is not

allergic in type [17, 54]. AR is commonly comorbid with asthma and frequently occurs prior to the development of BHR [4].

The fact that the entire airway may become inflamed in both AR and asthma may be explained as either because the allergenic trigger reaches the whole airway or that an allergic reaction in the nose affects the bronchi due to interaction with the nose. Research that compared nine cases of grass pollen-sensitive AR with nine healthy volunteers used an allergenic challenge to the nose to resolve the issue [57]. The challenge resulted in worsening of nose-related symptoms alongside symptoms related to the bronchi. Furthermore, sufferers from AR had a peak expiratory flow rate below that found in the healthy group. The AR group had higher numbers of eosinophils and greater expression of VCAM-1 (vascular cell adhesion molecule-1) in the mucosa taken from the bronchi. The bidirectional nature of nasobronchial interaction was then demonstrated when segments of the bronchi were separately challenged, in a reversal of the earlier phase in the experiment [48].

Hay fever cases with asthma who were supplied with placebo had inflammation affecting the distal airways. The sputum had raised numbers of eosinophils. Whilst nasal topical steroid (fluticasone propionate) treatment resulted in decreased eosinophil levels, there remained a significant elevation above the baseline level. Inhaled steroids by mouth caused greater reduction in sputum eosinophilia than topical treatment, and combining both modalities was the most potent in terms of reduction in eosinophilia and managing asthma symptoms most effectively. To enlarge on these findings, greater numbers are needed and for lengthier periods of follow-up, as well as consideration of other factors, such as asthma attacks, to allow a higher-powered analysis to be performed [1].

40.6 The Link Between Rhinosinusitis and Asthma

In a child, having a disorder of the paranasal sinuses is considered to predict the risk of developing disease of the distal airways, such that rhinosinusitis and asthma may be thought of as different phenotypes of the same pathological mechanism [58]. Researchers have recently come to see inflammation as the key facet to appreciating the pathophysiology of these diseases. However, other factors producing interactions of the proximal (nose, sinuses, pharynx, larynx and trachea) and distal (bronchi and lungs) portions of the airway may also be of significance [59]. The co-occurrence of sinusitis with asthma may reflect an epiphenomenological linkage [60]. Some 34–50% of asthma sufferers have comorbid rhinosinusitis [61].

The connection between rhinosinusitis and asthma might be due to a nasobronchial or pharyngobronchial reflex; postnasal drip and aspiration into a distal airway; breathing in cold, dry air or air pollution; or an underlying pathogenetic basis that is common to both disorders [62]. The same indicators that clinicians use to assess bronchial inflammation in asthmatics also have a correlation with how severe sinusitis is [63, 64].

Both diseases feature airway mucosal inflammation, with prominent eosinophilia. Eosinophils seemingly injure the mucosa when they excrete cytokines,

alongside other immune signalling molecules. This injured mucosa secretes yet more cytokine and chemokine signals, drawing the attention of eosinophils. Thus, a vicious cycle is set up whereby inflammation keeps worsening [63, 65]. Patients with nonsteroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD) experience worsening of symptoms of both rhinosinusitis and asthma after ingestion of NSAIDs, the fact that also supports one airway concept [66].

40.7 Conclusion

The concept of united airways appears valid, especially for AR and asthma. Other local organs, eyes, ears and throat, may also be affected. Thus every patient presenting with airway disease should have a comprehensive history and assessment of upper and lower airways.

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Does Rhinitis Pharmacotherapy Improve Control of Comorbid Asthma?

41

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41.1 Introduction

Allergic rhinitis (AR) is one of the most prevalent chronic diseases, with a frequency of between 3 and 19% in various countries [1]. AR displays heterogeneity, encompassing seasonal (SAR) and perennial (PAR) variants. According to one study, around 10% of people suffer from SAR, whilst between 10 and 20% experience PAR [1]. These estimates may be too conservative: Meltzer [2], for instance, puts the prevalence of AR at 25% of the general population, but as many as 40% of children may be affected.

Asthma similarly displays heterogeneity. Wenzel [3] even went so far as to claim that defining asthma is difficult because of the fact that it is so complex, reflecting a range of overlapping syndromes. The majority of ways of defining asthma rely on a symptomatic pattern (wheeze, shortness of breath) reflecting pulmonary dysfunction and a relapsing tendency, together, possibly, with consideration of treatability (such as response to steroids) [3]. The prevalence has been put at between 4 and 11% of the general population [4]. Canadian research indicates that failure to treat the condition to the recommended levels remains common [5, 6].

The scientific literature reflects a growing acknowledgement that asthma and AR are connected. Nonallergic asthma and nonallergic rhinitis will not be discussed here, except to note that it is common for sufferers from nonallergic asthma to also experience nonallergic rhinitis, with or without rhinosinusitis. Whilst these

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_41

associations are not as strong as that between allergic asthma and AR, some researchers have discovered links [6].

It is plausible to envisage that the different sections of a single passageway with no interruptions leading from the nostrils to the deepest part of the lungs should share many similarities. In the following sections, the epidemiological, pathophysiological and therapeutic aspects will be discussed. Several different agents are available to treat the airway diseases. Asthma, for example, can be adequately controlled using corticosteroid inhalers and beta$_2$-agonists bronchodilators, in most cases, but may benefit of immunotherapy or new biological treatment in specific cases as indicated by the Global Initiative for Asthma (GINA) [7].

41.2 Allergic Rhinitis and Asthma Comorbidity

Asthma is a disorder usually characterised by chronic inflammation of the airway mucosa of the bronchi and also the more distal airways, featuring a varying (and often remediable) degree of airflow limitation, hyperreactivity of the bronchi and periodic flare-ups, in which respiratory difficulties, such as wheeze, cough with sputum, shortness of breath and a tight chest, are the most common symptoms [7, 8]. AR, which may occur together with conjunctivitis, affects the supralaryngeal portion of the airways and is triggered by the nasal epithelium coming into contact with allergens, thus provoking an inflammatory response initiated by specific IgE. Patients complain of nasal discharge, pruritus, sneeze and blockage of the nose [8, 9]. There is a similar inflammatory pattern in both regions of the airway, if AR or asthma is chronic or when allergens are deliberately presented to the airway mucosa in a provocation test. In both conditions, there are indications of a systemic inflammatory response that may lead to eosinophilic inflammation of the entire airways. Asthma and AR are frequently found together [9, 10], and AR is a strong predictor for asthma [11].

The co-occurrence of asthma and AR has been demonstrated on multiple occasions by epidemiological studies. The older research suggested that asthma was found in 40% of cases of AR, whilst AR was found in between 30 and 80% of cases of asthma. Simons argues that the older studies give too low prevalence figures, since newer studies with interview techniques capable of greater sensitivity put the prevalence of AR at 98.9% amongst those with atopic asthma and at 78.4% in those with non-atopic asthma [12]. Leynaert and colleagues [13] have published a review of a number of studies that indicate that rhinitis and asthma are strongly associated, whether the individual is prone to atopy or not.

The last decades have witnessed a considerable rise in the number of cases of both AR and asthma in western Europe and the Anglosphere [4]. In Canada, for instance, the prevalence within the general population went steadily up from 6.4% in the period 1995–1996 to reach 8.4% in the period 2000–2001. This increase was particularly evident in females. In 1995–1996, 6.7% of females suffered from asthma, but by 2001, the frequency was 9.9% [14]. A similar picture has emerged from a number of studies looking at the frequency of AR, with the data telling a comparable tale of increase [15].

41.3 Pathophysiology

The histological appearances of the normal mucosae within the nose and the bronchi share many features. The external nostrils, which produce keratin, and the nasopharyngeal and laryngeal mucosae, with their stratified squamous architecture, are unusual for the airway. Elsewhere in the tract, the mucosa is seen to be a pseudostratified epithelial layer atop a reticular basement membrane, with an adjacent lamina propria. The epithelial layer consists of column-shaped cells bearing cilia, with goblet cells dotted between [16], whereas the subepithelial layer bears blood vessels, fibroblasts, nervous tissue, mucus-secreting glandular tissue and cellular components of the immune system. The nasal lining differs from the bronchi by having more abundant capillary vessels in the submucosa and by possessing the sinusoids, which can fill with blood from the veins. The bronchi have a ring of smooth muscle around them, a feature lacking in the nasal lining [16, 17].

When allergens come into contact with the mucosal lining of the nose, an inflammatory response begins, with the early-phase reaction progressing on to late-phase reaction in some occasions and certain patients. Mast cells that have undergone prior sensitisation by specific IgE (sIgE) degranulate in response to the contact between the allergen and sIgE, which cross-link the IgE receptors in the surface of the mast cells, releasing in the process pro-inflammatory molecules, such as histamine, prostaglandin D_2, cysteinyl leukotrienes and neutral proteases [9, 18]. These signals activate sensory neurones, thereby causing capillary leakage and producing symptoms: pruritus, sternutation, rhinorrhoea and nasal blockage. The other cellular components involved in allergy are dendritic antigen-presenting cells known as Langerhans cells and T_{helper} (T_H) type 2 lymphocytes, which drive sIgE synthesis. As inflammatory cells (eosinophils, basophils and T-lymphocytes) become increasingly recruited and activated, yet more histamine is released, alongside the leukotrienes, pro-inflammatory cytokines and chemokines, ensuring the reaction to the antigen continues and leading up to the late-phase reaction, which begins between 6 and 9 h after the typical immediate early-phase response [19, 20].

The trachea and bronchi contain evidence of both inflammation and microanatomical alterations (“remodelling”) in asthmatic individuals. It is usually accepted that remodelling can only occur following persistent inflammation involving eosinophils. Animal models lend weight to this theory [21]. It is currently an unresolved issue whether remodelling precedes or follows persistent inflammation in man [22–25]. However, this understanding is a necessary prerequisite if interventions are to be timed so as to prevent the development of inflammation and remodelling that occur in asthmatic individuals. This approach also holds out the promise of being able to tell which children who wheeze at kindergarten age will go on to develop full-blown asthma [26]. It is noteworthy adult-onset asthma has been increasingly reported amongst subjects with severe asthma who have partially irreversible airway obstruction, indicating considerable remodelling [26].

Inflammatory changes within the airway may be seen even in cases where respiratory function parameters are within normal limits, but asthma-associated symptoms are present [27]. Thus, FEV_1 is not an accurate measure of current or future inflammatory changes in the airway. On the other hand, infants who qualify as

asthmatic on clinical grounds (i.e. they demonstrate reversibility of airway blockage) may show evidence of neither eosinophilic infiltration of the bronchi nor structural changes [23]. Since both pathological features are already present to an advanced degree in severely asthmatic children at a median age of 10 years, the onset of this process must be at an earlier age [22]. Indeed, recently, evidence has emerged that the pathophysiological changes begin by the age of 1–3 years, with infiltration of the tissues by eosinophils being correlated with a thickened reticular basement membrane [25].

The most obvious way in which AR and allergic asthma are similar is that both disorders involve an immunological response to a particular antigen. This reaction by the immune system is usually termed "allergy", with the antigen labelled in this instance as an "allergen". Kay [19] has observed that the original meaning of the term "allergy", when used by Clemens von Pirquet in 1906, was to describe an immune response to an antigen, whether noxious (i.e. a protective reaction) or harmless (i.e. a pathological reaction). This latter type alone, representing a type 1 immune hypersensitivity, is what "allergy", as currently used, refers to.

Where airborne allergens are encountered, immunoglobulins (antibodies) to the allergen may be formed. It appears that genetics plays a role in how susceptible an individual is to synthesising excessive volumes of immunoglobulin, especially IgE, to a particular allergen. When this does occur, sensitisation to an allergen takes place, resulting in synthesis of targeted sIgE, which is bound to the IgE receptors at the plasma membrane of mast cells within the mucosae [2].

How the inflammation occurs shares similarities in AR and asthma. This is linked to the similar histological features of the airway—pseudostratified epithelia of columnar type, bearing cilia and with interspersed goblet cells [12]. Likewise, the basic pathophysiology of both conditions involves localised secretion of pro-inflammatory signals followed by a systemic response in which eosinophils migrate to the site of reaction. At the beginning, AR usually results in initial sneezing, nasal discharge and conjunctival congestion, whereas asthma causes wheeze, cough and dyspnoea, accompanied by airflow limitation that can be objectively assessed. The early and late phases of both disorders follow a similar sequence and have similar timing. Around 60 min after allergenic exposure, AR symptoms are maximal. At the same time point, asthmatic individuals are subject to a rapid deterioration in respiratory function, reflected in changes in FEV_1. Whilst the late-phase allergic response is occurring, individuals with AR have a persistent nasal obstruction, corresponding to a sustained decline in pulmonary function in individuals with asthma. Following the interruption of the exposure to the allergen, symptoms of both conditions tend to resolve within a 12- to 24-h time period, but persistent inflammation and hyperreactivity may remain [7].

In allergic asthma, aeroallergens inhaled through the bronchi may go through the epithelium by passing between the tight junctions binding the epithelial cells at their apex or may be actively engulfed by the cells. As with nasal allergic reactions, both an early and delayed phase to the reaction may be discernible. Binding of allergenic epitopes leads to cross-linkage of mast cell membrane-bound sIgE, followed by release of stored histamine and tryptase and activation of the arachidonic acid

metabolism with the generation of prostaglandins and leukotrienes, which results in the capillaries becoming significantly more leaky, migration of inflammatory cells to the area and yet further secretion of messengers promoting further inflammation [26].

The major cell type involved in promoting a persistent inflammatory response in asthma is the CD4+ T_H cell, which synthesises the cytokine regulatory molecules, interleukin-5 and interleukin-4 (IL-4, IL-5). Circulating IL-5 is one factor responsible for the recruitment of eosinophils from the bone marrow. Eosinophils bind to adhesion molecules expressed on the bronchial capillaries in response to TNF-α (tumour necrosis factor alpha) and IL-4 release. After pavementing occurs, the eosinophils are induced to enter the epithelium and traverse to the luminal surface by chemotactic molecules released by the epithelium itself, as well as the immune system. Eosinophils, having undergone activation, secrete cytotoxic compounds in granular form. These compounds weaken the epithelial cells and cause them to break away from neighbouring cells. Within the lumen, these damaged cells are found alongside eosinophils and high levels of mucin [26]. Whereas CD4+ Th cells represent adaptive immunity and a typical specific allergic response, it has been more recently recognised that in asthma, the stimulus for production of IL-5 and subsequent eosinophilic inflammation may also result in an activation of the mucosal innate immunity involving the release of "alarmins" (TSLP, IL-33 and IL-25) and activation of innate lymphoid cells type 2 [27, 28].

41.4 Interactions Between Asthma and Allergic Rhinitis

Many researchers view AR and allergic asthma as two different ways in which an identical underlying disorder, the chronic allergic respiratory syndrome, may present [29, 30]. The strong epidemiological evidence supporting the unity of these two diseases has been presented elsewhere [31]. It can also be noted that sufferers from AR often also have bronchi that are hyperreactive or present signs of small airway obstruction [31], despite an apparent absence of asthmatic symptomatology. Inflammatory changes can be induced in the bronchi of such patients by nasal allergenic provocation [32]. Conversely, nasal eosinophilia is demonstrable in asthmatic individuals who are asymptomatic for AR [29, 30]. Individuals who have AR but not asthma also responded to allergenic challenge in one segment of the bronchi by developing an inflammatory response within the nose [33, 34]. Despite this experimental evidence, asthma is not invariably present in cases of AR, nor AR in cases of asthma. Some of these apparently exceptional cases have a genetic basis. An example occurs when particular haplotypes associated with the recently discovered GPR154 gene located on chromosome 7 are present. These haplotypes result in susceptibility to AR, but not to asthma [35].

There are a variety of mechanisms which may account for how AR produces a diseased state in the more distal airway. One such mechanism is that loss of the conditioning function on inhaled air normally performed by the nose. Another is a reflex mediated by the nervous system that links upper and lower airways. Nasal

secretions may also be aspirated lower down the respiratory tree and produce irritation. Finally, one part of the airway may provoke a systemic inflammatory response, dependent on humoral factors and bone marrow involvement, that ends up involving other portions of the airway. This latter has been termed "systemic cross-talk" [29, 32, 36].

41.5 Treatment Approaches for Allergic Rhinitis and Asthma

AR and asthma share many features in common to suggest they belong to one only syndrome. The pathophysiological basis of asthma and AR is similar, and the different patterns in symptoms involved can be explained by anatomical differences in the affected organs. In both conditions, inflammation develops in a similar fashion, with the mucosae of both the nose and bronchus exhibiting eosinophilia. They are both becoming more frequent, they affect quality of life to a comparable extent, and they lead to important comorbidity. AR is frequently seen before asthma develops. The economic consequences of asthma and AR are both considerable, on an individual and societal level [7].

The fact that asthma and AR can both be treated in similar fashion is also suggestive of a close similarity between the two conditions. Guidelines for management pay attention to this connection and advise assessing patients presenting with asthma for AR and vice versa. Pharmacotherapy should aim to treat both disorders simultaneously for maximum control and to reduce the number of agents needed for treatment [34]. It is plausible that treatment guidelines may eventually suggest a goal of managing the entire respiratory system at once. Such a development would pave the way for a fully inclusive view of personalised holistic management of both the upper and lower airway [7].

Benefit in inflammation associated with AR has been demonstrated in a recent review for the following agents: topical nasal steroids, histamine blockers and montelukast. The latter is a leukotriene receptor antagonist (LTRA) [37].

Inhaled corticosteroid (ICS) agents are employed in asthma. In the short term (days to weeks), they dampen inflammatory responses in the bronchi, whilst in the longer term (more than 1 year), the reticular basement membrane is seen to reduce in thickness [38]. Montelukast is associated with a reduction in the level of circulating eosinophils, as well as those found in induced sputum [39]. After a treatment period of 4 weeks with the LTRA, pranlukast, the level of inflammation observed within the bronchi, as assessed histologically, was reduced [40]. Leukotrienes have been shown to promote the growth of leiomyocytes and their migration in vitro. LTRA application reduced this action by leukotrienes [41–43].

Research carried out in the early 1990s demonstrated that inhaled corticosteroids led to an improvement in clinical presentation [44, 45]. The Finnish asthma program, dating from 1994, was an initiative aiming to reduce the disease burden from asthma in Finnish patients. Treatment focused on reducing inflammation and was delivered through asthma specialists teaching family doctors, nurses and pharmacists. This initiative has been credited with reducing asthma-related hospitalisation

and mortality over a decade [46]. The benefit has stemmed mostly from more targeted and earlier pharmacotherapy aiming to reduce inflammation [26]. A similar benefit has been demonstrated by a citywide programme in Brazil [47].

The Canadian Rhinitis Working Group and the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative workshop have put forward guidelines on managing AR and asthma [8, 48]. Van Cauwenberge et al. have produced a consensus statement which emphasises the necessity of distinguishing AR from other disorders that may co-exist with it [15]. If an allergenic culprit has been identified, avoiding exposure to the allergen is the initial action required, although Platts-Mills [49] is obviously correct in stating that avoidance is more easily advised than achieved. The co-occurrence of asthma and AR, and their symptomatic overlap, suggests the clinical logic of evaluating both disorders at the same time. Indeed, hopes for a rationally based approach to management depend on acknowledging that AR and asthma share a pathophysiological basis.

Pharmacotherapeutic interventions have principally aimed at antagonising the actions of pro-inflammatory mediators produced by the allergic response of the mucosa. Histamine is the most studied amongst pro-inflammatory substances. However, whilst antihistamines possess high efficacy in symptom reduction generally, their action on nasal congestion is disappointing [15]. To better deal this issue, a decongestant given orally (such as pseudoephedrine) may be given at the same time as the antihistamine with caution for a few days.

Another approach to reducing nasal congestion associated with AR is the use of a topical nasal steroid. Spray preparations are available that deliver the agent in wet or dry powder form. They are potent anti-inflammatory agents which work by preventing the secretion of cytokines and chemokines and reducing inflammatory cell recruitment to the epithelium [15]. Minshall et al. [50] have evaluated the effect of mometasone furoate intranasal spray on the nose lining. Histological evaluation indicated that inflammation had been dampened down without the development of concerning histological abnormalities, including when treatment occurred over prolonged periods. ICS therapy also possesses efficacy in reversing constriction of the bronchi occurring in asthmatic individuals.

In a meta-analysis, montelukast was observed to lessen nose-related symptoms during the day to a significant degree. Subdividing the whole group of patients into thirds on the basis of mean pollen exposure leads to the result that montelukast possessed differing degrees of efficacy for each tertile. The least exposed group gained no additional benefit of montelukast compared to placebo, although the medium- and high-level exposure groups did have significant benefit [49, 51]. Mucha et al. [51] pitted a 10 mg dose of montelukast (LTRA) against 240 mg of pseudoephedrine (decongestant) in the morning for a 2-week period in which the allergen was most prevalent in subjects with seasonal allergic rhinitis. Improvement was seen in both groups in terms of decreased allergic rhinitis symptoms, life quality and patency of the nasal airway. This evidence that montelukast possesses may be useful in subjects with seasonal allergic rhinitis presenting nasal obstruction when the burden of allergen exposure is highest.

LTRA agents possess proven efficacy in asthma. Barnes et al. [52] studied the efficacy of montelukast in cases of chronic asthma with mild severity, concluding that it offered benefit (FEV_1, e.g. demonstrated a 7–8% improvement compared to baseline). In certain individuals whose asthma is stably controlled by ICS, montelukast offered supplementary benefit in lessening inflammation, and quality of life was also rated higher [53]. Barnes et al. [54] also conducted a survey based on how montelukast was typically used on a national basis. The most benefit was seen in individuals with asthma of mild to moderate severity. Montelukast emerged from the survey as an agent possessing efficacy and with a high level of tolerability.

Meltzer [2] looked at how effective LTRAs are in asthma therapy in a review of research carried out on the agents zafirlukast and montelukast in asthma. The use of LTRAs in AR was also examined, and evidence adduced to show montelukast possesses benefit in treating AR.

Other studies have looked at the efficacy of LTRAs in cases of combined AR and asthma. Piatti et al. [55] observed cases of both AR and asthma during the allergenic exposure period. They discovered that zafirlukast produced a significant ($p \leq 0.05$) reduction in the symptoms of both conditions, implying a role in treatment of both AR and asthma.

A further study, this time by Philip et al. [4], assessed the efficacy of montelukast in individuals with symptoms of AR during the pollen season, as well as asthma symptoms. The study was carried out at 52 locations in America and in Europe during the spring and autumn of 2003. There were randomisation, parallel grouping, double-blinding and use of double-dummy treatments. Two groups each received either montelukast ($n = 415$) or placebo ($n = 416$) for an initial run-in time of between 3 and 5 days. There was single blinding. This period was followed by a fortnight of montelukast therapy, administered at night. Trial participants rated their symptoms on a daily basis and kept a diary. The primary outcome measure was the daily rhinitis symptomatic score, a composite of both diurnal and nocturnal symptoms. In cases of seasonal AR and active concurrent asthmatic symptoms, montelukast possessed significant efficacy in controlling AR symptoms. The primary outcome measure results revealed superiority of montelukast over placebo, and this result was significant ($p \leq 0.001$). Placebo did, however, have a large effect. This superiority was seen in both diurnal and nocturnal symptoms. Furthermore, when subgroup analysis was carried out, using asthma status at study initiation as a differentiator, the benefit on symptoms of AR was highest in those patients using ICS, with symptoms of asthma appearing at least twice weekly, with a value for FEV_1 below 80% of the predicted value and with at least 12% reversibility in airflow limitation produced by $beta_2$-agonist at the outset of the trial [4]. These data have been interpreted to mean montelukast possesses the highest efficacy in individuals whose asthma is more symptomatic.

Research aiming to identify targets for symptomatic relief in AR and asthma has focused on the CysLTs, a component of the humoral immune response. It has already been proven that blockade of CysLTs offers symptomatic and functional

benefit. Neither corticosteroids nor antihistamines can antagonise the leukotrienes; however, montelukast can achieve this. Not only does montelukast improve AR symptoms, but it possesses a comparable role to that of antihistamines and decongestants given orally. Montelukast works in both seasonal and perennial AR, as well as restoring pulmonary function in asthmatic individuals. Montelukast has demonstrably superior efficacy when allergens are most prevalent or asthma is more symptomatic. Because of this, montelukast is recommended in the management of both AR and asthma, preferentially in cases of mild asthma [7].

Individuals in whom AR and asthma co-exist may benefit from better asthma control through treatment of AR [9]. As outlined earlier, managing AR can reduce admission to hospital due to asthma, as well as attendance at accident and emergency departments [31, 56]. Montelukast is associated with improvement in pulmonary function in cases of AR [57, 58], and AR symptomatic scores, as well as global perceptions of asthma by both doctors and patients, improve when montelukast is administered to cases with both conditions [59].

The World Allergy Organization and the World Health Organization have just brought out Guidelines for the Prevention of Allergy and Allergic Asthma, with a focus on primary, secondary and tertiary prevention strategies [60, 61]. The guidelines contain the recommendation to address disorders of the proximal airway, in particular AR, to halt the progression towards asthma. Confirmatory proof that this strategy is effective in actual patients is largely unavailable. However, some data do suggest pollen immunotherapy aiming to treat seasonal rhinoconjunctivitis can render paediatric asthma less probable [62], yet even this is not direct confirmation that the "allergic march" is a preventable condition. Tertiary prevention, as outlined in the World Allergy Organization/World Health Organization guidelines, refers to the prevention of flare-ups and deterioration, with an emphasis on addressing the inflammation lying at the core of asthma [26].

The increasing awareness that inflammation is linked to the remodelling seen in asthma has led to a focus on addressing inflammation when managing these disorders. Individuals with apparent symptoms of asthma need to be investigated without delay to assess for underlying inflammatory processes and remodelling. In this way, therapeutic management can address inflammation, whenever it appears and whatever the level of severity. The first-line treatments are anti-inflammatory agents such as ICS or LTRA, for asthma that is mild, or ICS where a greater severity of disease exists. Typically, a short-acting beta-2-agonist is adjunctively prescribed for use as needed. As the disorder moves to moderate or severe, a long-acting beta-2-agonist (LABA) combined with ICS is given for routine use in adults and children >5 years. A strategy of prescribing an ICS with an LTRA has the advantage of managing symptoms along the entire length of the airway, but may be inferior to the combination of a LABA + ICS for symptom control and lung function improvement in asthma. In the light of the commonalities seen within the pathophysiology of AR and asthma, a holistic approach to the airway (plus the skin, in certain cases) may be the most beneficial way to proceed [26].

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Chronic Cough: Pathology, Causes and the Role of Rhinitis/Rhinosinusitis

42

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42.1 Introduction

Chronic cough is generally defined as a cough of over 8-week duration. For the purposes of this chapter, we will consider patients as having had a normal chest X-ray and spirometry as first-line investigations for their cough. We will also assume an absence of 'red flags' such as haemoptysis, weight loss, fever, hoarseness, prominent dyspnoea, 30-plus pack-year smoking history, current smoking and new cough/new voice changes in a smoker, dysphagia, recurrent pneumonia and others, as described by Irwin and colleagues (Irwin R, French C, Chang A, Altman K, et al. Classification of cough as a symptom in adults and management algorithms. CHEST Guideline Expert Panel Report CHEST. 2018;153(1):196–209).

Although progress has been made in comprehending the pathophysiology of coughing, treating cases where coughs are persistent remains a challenging affair. For the sufferer, chronic coughing may lead to significant discomfort and a reduced life quality [1]. Clinicians may incorrectly conclude, on the basis that the cough does not respond to pharmacotherapy, that its basis is functional, i.e. psychological in nature. There are several factors which render the treatment of cough challenging. In a number of individuals, an insufficiently comprehensive diagnostic workup, without due attention to causes both within and outside the lung, may cause treatment problems [2, 3]. In others, pharmacotherapy may involve doses that are too

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_42

low, or the course may be too short. There is evidence that chronic coughing can lead to the development of increased sensitivity of the cough reflex, leading to exaggerated cough responses and what has come to be known as cough hypersensitivity syndrome (CHS).

The seminal work on assessing and managing cough is by Irwin et al [4] They advocated a step-by-step method to assess the cause of coughing, which isolated a cause in approaching 98% of cases. The most frequent causes of chronic cough have been considered to be upper airway cough syndrome (UACS), a large contributor to which is postnasal drip syndrome (PNDS), asthma and gastro-oesophageal reflux disease (GORD/GERD); additional causes include, amongst others, eosinophilic bronchitis (EB) and medication side effects, particularly ACE-inhibitor-induced cough [4] (Alan G. Kaplan, Pulm Ther (2019) 5:11–21). This approach has been found to have ongoing validity, both by the same researchers [5, 6] and others working in hospitals [7, 8]. The stepwise approach has not been altered and is now part of the recommendations for treating cough supplied by the American College of Chest Physicians [9].

Whilst it has been generally accepted that the stepwise diagnostic assessment addressing causes both within and without the lung is effective, some researchers have nonetheless questioned whether the three causes (CVA, PNDS and GORD) can really explain virtually all persistent coughs [10, 11]. It has been reported that 12–42% of cases of persistent cough remain undiagnosed or untreatable, even where this approach is followed [12–14]. Undiagnosed persistent cough has been variously interpreted as either the frequency of cough hypersensitivity syndrome (likely equivalent to what has previously been labelled as idiopathic cough [14]) or as the result of inadequate length of treatment trials or doses in managing patients [15, 16].

42.2 Pathophysiology

Coughing is under the control of a reflex, with the afferent portion consisting of cough receptors, sensory nerve fibres and the centrally located cough centre within the brainstem and the efferent (effector) pathway. The afferent portion principally involves the vagus nerve but also the trigeminal and glossopharyngeal nerves; the efferent portion the vagus, phrenic and spinal motor nerves. The reflex can be modulated at any point on the arc. Hence, a deeper understanding of the physiological function and dysfunction of the cough reflex is essential to effective therapy. There is some dynamicity in the fibres comprising the afferent pathway, and the way that certain fibres become active following sensitisation to particular stimuli, such as inflammation of the airways, has been referred to as ‘plasticity’ [17]. Whilst viruses are a key reason for cough to develop and are often cited in cases of chronic coughing (postviral chronic cough), it is not well understood how viruses affect the sensitivity of the cough reflex. Rats infected with the respiratory syncytial virus had higher levels of tachykinin in lung tissue, as well as of neurokinin-1 (NK1), which acts as a receptor for substance P [18]. Chronic coughing may also lead to central changes, in the brainstem cough centre, which may further exaggerate cough hypersensitivity.

There are key differences in the neuroimmune function of the airway in males and females. Research has shown that women are more susceptible to triggering of the cough reflex, both in health [19, 20] and disease [21]. These sex-related differences are not seen before adulthood, which may indicate a role for sex hormones in regulating coughing [22].

42.3 Causes for Cough Including Rhinosinusitis

Research carried out prospectively has ascertained that between 92 and 100% of persistent cough in nonsmokers whose chest X-ray is normal is attributable to just three conditions [23]. The following are in order of occurrence [24]:

1. Upper airway cough syndrome (UACS), including postnasal drip syndrome (PNDS)
2. Asthma
3. Gastro-oesophageal reflux disease (GORD)

42.3.1 Upper Airway Cough Syndrome

UACS involves feeling sinonasal secretions dripping into the pharynx, accompanied by rhinorrhoea and needing to keep clearing the throat. The diagnosis depends on a history of appropriate symptoms, with corroborative physical findings rarely being discovered. Twenty percent of UACS cases are in people who lack awareness of postnasal drip and do not associate it with coughing [25]. Finding mucus within the oropharynx or the presence of oropharyngeal cobblestones is at most suggestive of UACS, as the finding, whilst possessing high sensitivity, lacks specificity [23].

The concept of PNDS has been widened in the definition of UACS, which now encompasses a wide variety of conditions of the sinus or nose that can cause coughing. Some examples are [23]:

- PNDS itself
- Acute bacterial sinusitis
- Allergic fungal sinusitis
- Allergic rhinitis
- Chronic rhinosinusitis (CRS)
- Nonallergic rhinitis
  - Nonallergic rhinitis with eosinophilia (NARES)
  - Occupational rhinitis
  - Postinfectious rhinitis
  - Rhinitis due to anomalous anatomy
  - Rhinitis provoked by physical or chemical irritation
  - Rhinitis medicamentosa
  - Rhinitis of pregnancy
  - Vasomotor rhinitis

Despite the above, it is to be noted that the vast majority of patients presenting to ENT clinics and/or allergy clinics with the above pathologies do not complain of chronic cough; rather they have the appropriate nasal and sinus symptoms associated with these conditions.

42.4 Approach to Treatment

Whilst some experts have claimed that the features of a cough offer little value diagnostically [26], from a clinical point of view, symptoms consistent with upper airway problems (see below) or suggestive of GORD should prompt pharmacotherapy for rhinitis/rhinosinusitis or reflux disease, respectively [27]. The ideal dosages to use and durations of treatment remain unclear, which is especially apparent if one considers the management of coughing linked to GORD. Whilst heartburn typically resolves over a brief period of days, the duration necessary to prevent coughing is apparently much lengthier, and the evidential support for effectiveness much less [28, 29]. Generally, a trial of treatment of a proton pump inhibitor is given for 6–8 weeks with consideration of the addition of a prokinetic agent such as domperidone or metoclopramide. Lifestyle measures and dietary modifications should also be recommended, including raising the head of the bed and avoiding eating for 3 h before bedtime. A small group of such patients, in whom antacid treatment for sufficient periods and at adequate doses has not resolved the reflux, may need to progress to a surgical approach [16, 30]. Whilst an empirical treatment approach is reasonable in those who have symptoms suggestive of reflux, failure to respond to these measures or an absence of typical symptoms should prompt attempts at obtaining a firm diagnosis, using dual-channel 24-h pH probe monitoring and/or oesophageal impedance monitoring.

A currently topical area of study is ‘nonacid reflux’. Irwin et al. [30] investigated eight cases of chronic cough persisting in spite of almost complete acid suppression by means of proton pump inhibitors, prokinetic agents and a diet aiming to reduce reflux (omeprazole 20–80 mg daily by mouth and cisapride 40–80 mg daily by mouth). This research found a role for anti-reflux surgery in ameliorating coughing which does not respond to pharmacotherapy. They note that surgery produced sustained benefit. Acid reflux disease in cases of both cough and GORD could be a misleading terminology given that nonacid reflux may actually account for why some individuals cough (i.e. volume reflux containing stomach enzymes, bile salts, etc.) [31]. If such a patient’s cough does not benefit from therapy for acid reflux, the cough is not necessarily idiopathic in nature [16].

Treatment with an inhaled corticosteroid is a reasonable empirical approach in a patient with evidence of airway obstruction on spirometry or with evidence of airway eosinophilia—increased sputum eosinophils (>3%) and increased exhaled nitric oxide (>50 ppb appears a sensitive cutoff, but levels >40 ppb might also prompt a trial); an elevated peripheral blood eosinophilia of greater than 0.3×10^9 cells per litre may also be a suitable surrogate for airway eosinophilia. In the absence of a response, further investigations to confirm or exclude a bronchial airway

component can include methacholine provocation testing. Failure to respond to inhaled corticosteroids despite a high level of suspicion of asthma as a cause should prompt checking inhaler technique, adherence and, potentially, a trial of oral prednisolone.

Non-asthmatic, eosinophilic airway syndromes may be a cause of chronic cough. These are diagnosed by analysing forced sputum or by bronchoscopy and lavage and/or bronchial biopsy [32]. The defining characteristics of eosinophilic airway syndromes are that the airway is inflamed by eosinophils, but there is no change in the function of the airway (i.e. no bronchoconstriction), unlike in asthma. The syndrome that has been best characterised so far is eosinophilic bronchitis (EB). EB is thought to explain 15% of cases with a specialist referral for persistent cough [33].

EB cases often benefit from steroid inhaler therapy. Given the fact that an empirical trial of steroids is common in primary care, calculating the precise frequency of EB is likely to be problematic. In a recent development, researchers in Japan have begun to speak of the 'atopic cough' syndrome [34]. This syndrome is characterised by coughing, no benefit from bronchodilators and inflammation of the trachea and bronchi which is composed of an infiltrate of eosinophils.

Treatment for UACS principally involves nasal and sinus 'douching' with warmed, physiological saline, as well as intranasal corticosteroids. Specific treatments may be tailored to different conditions, for example, 'vasomotor' rhinitis may respond well to intranasal ipratropium bromide spray; if postnasal drip from this condition was the cause or an exacerbating factor in a chronic cough, then the cough may be expected to improve. Whilst surgery may improve the congestion and facial discomfort seen in chronic rhinosinusitis, it less frequently improves patients' complaints of postnasal discharge.

42.5 Failure of First-Line Therapies and Next Steps

The frequently encountered reasons for inaccurate diagnosis or ineffective management of chronic cough are listed here: not initiating an empirical treatment trial for UACS since there were no aspects of the history or examination that pointed towards upper airway cough syndrome, not undertaking imaging of the sinuses in cases where there is latent sinusitis, not attempting a bronchial provocation test to detect asthma, insufficiently attempting a trial of treatment for presumed cough-variant asthma, not assessing thoroughly a patient with GORD and suboptimal treatment of GORD. These latter two situations are often the result of a clinical picture that lacks the classical hallmarks of GORD. Rare causes of chronic cough may also have been missed, such as latent cardiac failure, interstitial pulmonary disease, neuromuscular disease, mild degrees of bronchiectasis, thyroid disease and an isolated abnormality within the bronchi like tumour, localised Wegener's granulomatosis, inhaled and lodged foreign objects and airway malacia [35].

Even with appropriate investigation and treatment of the three common causes of chronic cough, there are nonetheless individuals whose cough ends up labelled as

may appropriately be termed ‘idiopathic’, though this probably represents individuals who have coughed for long enough to induce neuroplasticity in their cough reflex arc and should properly be labelled as having cough hypersensitivity syndrome (CHS). A study with a case-control methodology that was recently published indicated that there was a female preponderance in ‘idiopathic’ cough (77%) and that this was associated with an eightfold increase in the risk of an autoimmune disorder affecting a single organ, mainly the thyroid [36]. There is an association between chronic cough and inflammatory disorders of the airway. Compared to normal controls, when induced sputum was tested, the titres of a number of markers known to be involved in coughing were raised in chronic cases [37]. These markers included the cysteinyl leukotrienes, histamine and prostaglandins D2 and E2. After asthmatic patients/those responding to inhaled corticosteroids were excluded, individuals with chronic cough without an underlying identifiable cause had higher histamine levels than those with a chronic cough of known cause (UACS, GORD, etc.) [37]. This finding fits with the results from an older bronchoscopy study [5], in which mast cell counts were raised in the bronchoalveolar lavage fluid. A study in which 19 patients lacking a diagnosis to explain cough, even after extensive investigation, underwent bronchoscopy [38] found that lymphocyte count was raised in bronchoalveolar lavage fluid, but not in the bronchial mucosa. Of two other small studies, one found no increase in lymphocyte numbers in the bronchi and alveoli [39]; but the other identified lymphocytic bronchitis when the bronchial lining was biopsied [40]. These results leave it uncertain as to what role lymphocytes may or may not play in chronic cough. One reason for the seemingly contradictory results may be that several different disorders may provoke chronic cough. It is worth considering that chronic cough could be composed of a discrete syndrome or may, more probably, consist of several different syndromes [35].

Treatments tried for underlying cough hypersensitivity syndrome as the cause of chronic cough have included gabapentin, amitriptyline and pregabalin—centrally acting drugs aimed at reducing overactivity of the cough centre in the brainstem. These drugs may all have significant side effects, however, with sedation often a problem. Other therapies have included inhaled local anaesthetics, an attempt to reduce the afferent sensitivity of the reflex. Opiates also have effective cough-suppressing effects in many patients, though constipation and dependence are frequent and potential problems, respectively. In the authors’ experience, speech therapy involvement and the instigation of active attempts to suppress coughing are the most helpful intervention in this group of patients, though this requires enthusiasm, effort and persistence on the part of patients. A combination of speech therapy and pharmacotherapy can also be tried.

ERS guidelines on the diagnosis and treatment of chronic cough in adults and children [41] recently divided chronic cough into seven different phenotypes:

1. Asthmatic cough/eosinophilic bronchitis
2. Reflux cough
3. Postnasal drip syndrome/upper airway cough syndrome
4. Iatrogenic cough

5. Chronic refractory (idiopathic) cough
6. Chronic cough in children
7. Chronic cough in other diseases

They developed new strategies for the diagnosis of these phenotypes and for the treatment approach [41].

Therapeutic strategy after the first three conditions may be an antitussive strategy for reducing the hypersensitivity by neuromodulation. Low-dose morphine, gabapentin and pregabalin are advocated, but they have a lot of side effects. Future pharmacological agents are drugs which tackle neuronal hypersensitivity. They block excitability of afferent nerves and inhibit targets such as the ATP receptor (P2X3) [41].

42.6 Chronic Cough in Children

The causes and treatment of cough differ in children from those in adults.

Most children cough with acute respiratory viral infections. In a Norwegian study of 400 children under 16 years, acute respiratory infections showed an incidence of 5.6% per month. Low fever, nasal discharge and cough were the most long-standing symptoms. After 3 weeks less than 50% of the patients were completely recovered. No serious complications or sequelae were recorded [42]. Since the average child has between six and eight viral upper respiratory tract infections per year [43], the EPOS criteria for chronic rhinosinusitis may well be met. Cough and rhinorrhoea are prominent symptoms in children with chronic rhinosinusitis (30–120 days) [44] although those with IgE sensitivity to allergens appear more likely to cough [45].

However cough may also indicate a serious underlying disorder, and so all children with chronic cough should have a thorough clinical review, including consideration of possible foreign body aspiration [46].

Treatment should be based on the underlying cause. There is no evidence for use of symptomatic relief medications such as antihistamines which may do harm, nor for an empirical approach based on the big three adult aetiologies.

Removal of environmental exacerbating factors such as tobacco smoke [47] or relevant allergens should be encouraged in all coughing children.

42.7 Conclusion

Coughing is under the control of a reflex, with the afferent portion consisting of cough receptors, sensory nerve fibres and the centrally located cough centres and the efferent (effector) pathway. A stepwise diagnostic assessment addressing causes both within and without the lung is necessary to clarify the pathology. Rhinitis and rhinosinusitis may have an important role in not clearly diagnosed or ‘idiopathic’ cough and should be ruled out in such cases.

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Occupational Rhinitis

43

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43.1 Introduction

The sensory organs can be affected by environmental conditions. A well-known example of this is the damage done to the hearing apparatus by excessive noise exposure, whether at home or occupationally. Similarly, the nose is prone to damage, both at home and at work.

Moscato defined in 2008 occupational rhinitis (OR) as an inflammation of the nasal mucosa due to causes attributable to a particular work environment [1]. Partly because of concerns about quality of life, the field of occupational rhinitis has gained importance in recent years.

Working environment concerns are increasingly a priority. Occupational health can have marked consequences on an employee's performance, leading to lower productivity and psychosocial difficulties. Hazardous work environments have generally been cleaned up, but there remain occupations where an odorous environment remains the norm.

Specific industrial chemicals, mixtures or dusts are known to cause work-related olfactory dysfunction. This is explained by the relatively direct exposure to the outside environment of the olfactory receptor neurons in the nose. Temporary or permanent work-related olfactory dysfunction can be induced by both acute and

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_43

chronic occupational exposure to irritants. In the past, there was little attention from the medical community for smell disorders in workers [2, 3].

It is noteworthy that olfaction is vital for survival in humans and animals. The sense of smell enables to detect and to enjoy food (digestive behaviour), to find a mate (social communication), to preserve happiness (limbic system) and to be aware of environmental hazards (warn about danger). Decreased olfactory function is an indicator of low levels of life expectancy. Olfactory disorders contribute to lower quality of life, reduced safety and poorer nutrition [4, 5].

43.2 Occupational Rhinitis

OR differs from work-exacerbated rhinitis (WER) in that the latter occurs when occupational exposure worsens an already existent rhinitis of allergic or nonallergic type, but is not the cause of the initial rhinitis [1].

Substances reported to cause occupational rhinitis are classified as high or low molecular weight (HMW or LMW) agents. HMW agents are inhaled allergens (e.g. latex, flour, laboratory animals) inducing an IgE-mediated allergic rhinitis. LMW agents are subdivided into two groups: sensitisers and irritants (Tables 43.1 and 43.2). The sensitisers are LMW agents that induce IgE-mediated immune response after a latency phase. In contrast, airway irritants are non-sensitizing LMW agents [6, 7]. A single exposure to high concentrations of an airway irritant induces an acute toxic effect on the nasal mucosa giving rise to transient or persistent rhinitis symptoms [8]. Long-term exposure to lower concentrations of airway irritants can induce a chronic dysfunction of the respiratory mucosa [9].

Epidemiologic data on the prevalence of occupational rhinitis are an underestimate. The lack of validated diagnostic tools plus reluctance of patients to complain about their occupational environment are explanatory factors [10]. OR is frequently seen in conjunction with occupational asthma (OA) [5]. It has been postulated that OR occurs two to four times more often than its asthmatic counterpart [1, 10] (OR leading to OA—please supply evidence cfr EAACI position paper on occupational rhinitis).

43.3 Work-Related Olfactory Dysfunction

Most papers on OR discuss classic ‘rhinitis’ symptoms as nasal blockage, rhinorrhoea, sneezing and pruritus. Quantitative or qualitative olfactory dysfunction as a symptom is regularly overlooked. Good data on the prevalence of work-related olfactory dysfunction is currently lacking [2]. It is been quoted that between 0.5 and 5% of all cases of olfactory dysfunction are secondary to occupational exposure [11, 12]. Cases of loss of smell that are classified clinically as ‘idiopathic’, and representing 10–25% of all cases of hypo- or anosmia, may also in reality include unsuspected instances of occupational toxic exposure [2, 13].

Table 43.1 HMW and LMW agents

HMW agents		
Flour	Mites	Latex
Laboratory animals	Seafood	Plants
Enzymes	Guar gum	Insects
Tobacco	Soya	Cattle
LMW sensitisers (LMW agents with latency phase)		
Isocyanates	Persulphate salts	Anhydrides
Aldehydes	Resins	Plastic
Polyurethane	Polyester	Polyamides
Acrylates	Amines	Plicatic acid
Metals: platinum, nickel, aluminium, cobalt, chromium		
Trees: mansonia, cedar, pine		
Drugs: piperacillin, morphine, tylosin, spiramycin		
Irritants (LMW agents without latency phase)		
Aluminium phosphide	Formalin	Phthalic anhydride
Ammonia	Fire/smoke	Sulphur dioxide
Bleaching agents	Hydrazine	Sulphuric acid
Calcium oxide	Hydrochloric acid	Tear gas
Carbon monoxide	Hydrofluoric acid	Trichloroethylene
Chlorine	Lithium hydride	Uranium hexafluoride
Chloropicrin	Metal fumes	Urea fumes
Diesel exhaust fumes	Metam sodium	
Diethylaminoethanol	Mustard gas	
Dinitrogen tetroxide	Nitrogen oxide	
Epichlorohydrin	Ozone	
Ethylene oxide	Perchloroethylene	
Hydrocarbons	Phosgene gas	

Common occupational agents, listed by molecular weight class
HMW high molecular weight, *LMW* low molecular weight

Table 43.2 Occupational agents

High molecular weight (HMW) agent	Low molecular weight (LMW) agent	
Animal proteins	Chemicals	
Plant proteins	Metals	
Enzymes	Wood dust	
	Pharmaca	
HMW allergens	*LMW sensitisers*	*LMW irritants*
(IgE-dependent)	(With latency phase)	(Without latency phase)

Intact olfactory function in order to perform their work is essential for some occupational groups (e.g. chefs, perfumers, sommeliers). Other occupational groups are dependent on olfactory function for their safety. If dangerous substances are no longer detected quickly enough, an olfactory dysfunction can also present a workplace hazard for the workers and the company (e.g. gas fitters, firefighters) [11].

Herberhold [14] identified various types of noxious stimulus that may lead to impaired olfaction, including thermal, mechanical and chemical types. In the latter case, greater chemical activity, smaller size and a longer length of time exposed are factors associated with greater olfactory dysfunction. Amoore [15] extracted virtually exclusively from case reports a list of agents for which the strongest empirical evidence was available [3]. Gobba [2] and Sundemann [16] have both written detailed overviews on the evidence concerning long-term harm (including olfactotoxicity) in workers exposed to metals and other chemicals.

In experimental trials, an animal is exposed to particular suspected chemicals in order to gain insight into the potential mechanism by which loss of smell occurs [16]. The histopathological damage is investigated at the level of the olfactory epithelium. Acute high exposure to reactive and soluble gas (e.g. chlorine, ammonia) induces lesions up to necrosis. Chronic exposure to airway irritants causes a spectrum of changes including inflammation, degeneration, atrophy, necrosis, keratinisation, hyperplasia, metaplasia and neoplasia [11]. In conclusion, most toxicants induce a toxic effect on the olfactory neuroepithelium. Some toxicants, especially nanoparticles, are suspected to access the brain from inhaled air via the olfactory epithelium and damage more central neural structures [3].

Governmental and non-governmental organisations apply ‘occupational exposure limits’. In work-related olfactory dysfunction, most damage is documented after an acute high exposure, where these limits were exceeded [3]. Various researchers [17, 18] have noted that coming into contact with multiple industrial chemicals, especially ones causing corrosion or irritation to the mucosae or to nervous tissues, is a factor in increased problems with olfaction. Most studies document the impact of one airway irritant on the nasal and olfactory mucosa. In real life, workers are intermittently exposed to multiple different specific environmental toxicants. Research establishing whether and to what degree this type of exposure cumulatively damages human olfaction is a challenge for the future.

43.4 Assessment of Olfactory Dysfunction

There is a wide variety in how humans perceive smells and tastes [1, 19]. The perception of smells is highly dependent on the country where the individual lives, their family background, lifestyle and traditions. It is normal for even healthy subjects to have a highly variable ability to perceive a monomolecular odorant [2, 20]. Research published recently has indicated that specific anosmia, in which a particular odour is undetectable by the patient, is vastly more common than was earlier thought to be the case [21, 22]. These are limitations that impact the reliability of olfactory testing.

Psychophysical tests that can quantify subjective sensory perceptions semi-objectively are validated in recent years. A wide spectrum of structured, practical, inexpensive, reliable test systems are in use: UPSIT (University of Pennsylvania Smell Identification Test), TDI Sniffin' Sticks test (Threshold, Discrimination and Identification Test), CCCRCT (Connecticut Chemosensory Clinical Research Center Test), Cross-Cultural Smell Identification Test, etc.

Work-related olfactory dysfunction is usually subclinical and can only be detected by an adequate assessment of the sense of smell. Different test methods are used in studies of workers exposed to industrial chemicals. This variety of methods applied in different studies affects the comparability of results [2]. Standardisation of procedures is paramount.

43.5 Conclusion

All human senses are valuable and their proper functioning has an effect on quality of life. Protecting the sense organs is vital, and olfaction (the fifth sense) is no different in this respect. Occupational risks to olfactory function need to be identified and managed carefully, and productivity goals should not be set at the expense of workers' sensory function. Standardised testing of the chemosensory function of the nose at regular intervals may identify problems before they become severe.

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Upper Airway Cough Syndrome

44

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44.1 Introduction

Coughing is one of the key natural ways the airway has to defend itself [1]. Mucus is secreted and then expelled by mucociliary clearance in healthy people. However, if the level of secreted mucus is such as to exceed the capacity of mucociliary clearance, coughing takes over as a key factor in expelling mucus. Occasional coughing is beneficial in removing debris and secreted substances from the lower airway and is beneficial in stopping infection. Cough, nonetheless, is amongst the most frequent of presenting complaints and may also herald a number of diseases affecting the respiratory tract, as well as other conditions [1, 2].

When assessing a patient complaining of cough, the first necessity is to clarify how long the cough has been problematic. Acute coughs have occurred for under 3 weeks, subacute coughing lasts between 3 and 8 weeks and chronic cough has a duration greater than 8 weeks [3–5]. Around 10–20% of people in general report having a persistent cough [6].

Coughing is principally beneficial in nature in that it functions to remove unwanted particles and pooled secretions from the lungs and the airways. Exactly how the cough reflex functions through neural control is still open to debate, although researchers typically agree that the cough reflex only involves afferent fibres of the tenth cranial nerve [7, 8]. The afferent fibres of this nerve consist of C-fibres, slow and rapid adaptive receptors (SARs and RARs) plus myelinated

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_44

nerves that end within the laryngeal, tracheal and bronchial mucosae, where they are referred to as cough receptors. It appears that the principal afferent fibres of cranial nerve X which produce coughing in man consist of C-fibres and mechanoreceptors [7, 8]. The afferents terminate in or near the medullary nucleus of the tractus solitarius. Central nervous system co-ordination of coughing occurs here.

Inflammatory responses to coughing may be a direct or indirect consequence. Smoking directly irritates the airways, setting up persistent bronchial inflammation, asthma and non-asthmatic eosinophilic bronchitis (NAEB). Secretions resulting from inflammation or acid reflux may be aspirated in small quantities, irritating the larynx and producing upper airway cough syndrome (UACS) and gastroesophageal reflux disease (GORD). The breakdown of pro-inflammatory signalling molecules is inhibited by ACEi (angiotensin-converting enzyme inhibitor) drugs. This means the airway becomes inflamed and the rise in pro-inflammatory signals may have a large role in upgrading how sensitive the cranial nerve X afferents are. Thus, the cough reflex is more easily triggered, and irritating substances, minor aspiration and the bolus effect of refluxate in the lower oesophagus can then set off coughing. There is a vicious circle in that persistent coughing injures the airway, leading to an inflammatory response, which then further heightens the coughing tendency [9].

A cough which endures more than 8 weeks is, by definition, chronic. Chronic cough has a variety of aetiologies, and in most instances several factors operate at once [10, 11] (Table 44.1). The most frequent reason for a persistent cough is upper airway cough syndrome (UACS), which used to be known as postnasal drip syndrome (PNDS). UACS is challenging to diagnose and manage, whilst at the same time, it can have a markedly negative impact on the sufferer's quality of life.

UACS may occur secondary to several diseases which affect the proximal airway, such as diseases of the nose or sinuses [12], anatomical anomalies, rhinitis (physical or chemical) or disorders affecting the pharynx [13–15].

44.2 Pathogenesis

Coughing in UACS is principally caused when the afferent arc of the coughing reflex is triggered [16]. Nasal or sinus secretions activate hypopharyngeal or laryngeal cough receptors [16]. More distally located cough receptors might also contribute, when there is micro-aspiration, but this has not been definitively shown so far [17].

44.3 Clinical Presentation

UACS is often associated with other less specific findings, such as drip into the posterior pharynx, needing to clear the throat often, rhinorrhoea, alteration in appearance of the lining of the oropharynx or mucus within the oropharynx [18]. Patients frequently report wheeze and recurrent infections of the upper respiratory tract, e.g. coryza.

Table 44.1 The aetiology of persistent cough

A. Diseases affecting the upper airway
– Upper airway cough syndrome (allergic and nonallergic rhinitis, chronic rhinosinusitis, etc.)
– Abnormal vocal cord function
– Neoplasia
– Presence of a foreign body in the airway
B. Diseases affecting the lower airway
a. Airway disorders
– Asthma
– Chronic bronchitis/COPD
– Eosinophilic bronchitis
– Bronchiectasis
– Cystic fibrosis
– Tracheomalacia
– Recurrent aspiration
b. Disorders of the pulmonary parenchyma
Pulmonary interstitial disorders
– Emphysema/COPD
– Sarcoidosis
– Lung infarction
c. Neoplasia
– Carcinoma arising from the bronchi
– Terminal bronchiolar carcinoma
– Non-malignant neoplasms of the airway
– Neoplasms arising from the mediastinum
d. Foreign body
e. Chronic infections
– Tuberculosis
– Mycological infections
C. Non-respiratory system origin
– Medication side effects: ACE inhibitors and β-blockers
– Oesophageal disorders: GORD, laryngopharyngeal reflux and fistulous connection between the trachea and oesophagus
– Psychological in origin

COPD chronic obstructive pulmonary disease, *GERD* gastroesophageal reflux disease, *ACE* angiotensin-converting enzyme

There is no objective test available to support the diagnosis, which is a clinical inference from the constellation of symptoms described.

As a clinical diagnosis, UACS depends on an appropriate history, physical examination, imaging and how the case responds to particular treatments.

The diagnosis is strongly supported by patients describing a sensation of a liquid entering the throat, nasal discharge and often clearing their throat. On occasion, there may be a history of snoring, wheeze and worsening of these problems when lying down.

Physical exam reveals pharyngeal oedema and cobblestoning of the mucosa in the posterior pharynx and nasopharynx. Secretions of a mucous or mucous and pus-filled type might be observed passing down the airway. However, not every case presents with secretions and the mucosa may seem healthy.

Computed tomography (CT) of the paranasal sinuses may indicate filled sinuses, thickened mucosae and an air-fluid level. To diagnose hay fever, skin prick or specific IgE tests may be of benefit. In a minority of cases of UACS, the history may be quite atypical.

44.4 Diagnosis

The differential diagnosis includes allergic rhinitis, perennial nonallergic rhinitis, postinfectious rhinitis, bacterial sinusitis, allergic fungal sinusitis, rhinitis due to anatomical anomaly, rhinitis due to physical or chemical irritation, occupational rhinitis, rhinitis medicamentosa and pregnancy rhinitis. GORD frequently gives rise to upper respiratory symptoms and can closely resemble UACS [17]. From prospective studies, it appears sinusitis explains UACS in 8–64%, perennial and nonallergic rhinitis in 37%, allergic rhinitis in 23%, rhinitis after an infection in 6%, vasomotor rhinitis in 2% and environmental irritation in 2% of cases [19].

44.4.1 Allergic Rhinitis

Allergic rhinitis (AR) is frequently the disorder responsible for UACS. When there is contact with an allergen, IgE binds to the allergen, and this triggers a cascade of immune reactions, resulting in oversecretion of mucus, amongst other effects. Typical allergens may be seasonal (such as pollen) or perennial indoor allergens (house dust mites, mould, cockroaches). Treatment of AR may involve topical nasal steroids, cromolyn, histamine blockers (topical or systemic) and leukotriene receptor antagonists. This is the first step in treating AR-related UACS. For certain individuals, a more lasting treatment may be achieved through allergen desensitisation procedures [20–22].

44.4.2 Perennial Nonallergic Rhinitis

Perennial nonallergic rhinitis is classifiable into vasomotor rhinitis and nonallergic rhinitis with eosinophilia (NARES).

Vasomotor rhinitis refers to a condition of uncertain aetiology wherein there is abundant, watery rhinorrhoea or nasal blockage, typically secondary to exposure to particular smells, temperature alterations or humidity changes. Some researchers suggest the pathogenesis depends on autonomic dysfunction [23, 24]. Cases do not

have an identifiable allergy, no infection is present, the anatomy is normal and no other systemic disorder is present.

NARES involves nasal and ocular pruritus and tearing. To make the diagnosis, eosinophilia must be demonstrable on nasal smear, but no allergy should be evident on skin prick testing and asthma should not co-occur [17].

44.4.3 Postinfective UACS

In postinfective UACS, the sufferer has recently recovered from an infective episode of the upper respiratory tract but is left with a dry cough that is not resolving. Dyspnoea may be present as well as wheeze, especially on expiration. The bronchial provocation test (BPT) may be positive, but this is temporary and does not indicate that asthma is present.

As well as in infective viral episodes, a persistent cough can develop with infections by mycoplasma, *Chlamydia pneumoniae* and *Bordetella pertussis* when catarrh is present [17, 25].

44.4.4 Chronic Rhinosinusitis (CRS)

CRS may present as a cough with sputum production, but equally there may be no symptoms other than a nonproductive cough. Paranasal CT imaging, endonasal endoscopy, allergy testing and antibody levels are suggested in the work-up for suspected CRS. Thickened mucosae, sinus fullness and an air-fluid level visible on CT imaging are suggestive of infection by bacteria, and hence antimicrobial therapy should be started. It needs to be observed, nonetheless, that a thickened mucosa in the absence of other signs is insufficient to diagnose infection [26, 27]. The most frequently encountered bacterial pathogens resulting in sinusitis are *Staphylococcus aureus*, coagulase-negative staphylococci, anaerobes, *Haemophilus influenzae*, *Moraxella catarrhalis* and several gram-negative rods [28].

44.4.5 Rhinitis Secondary to Anatomical Anomalies

Rhinitis may be secondary to anomalous anatomy, such as deviation of the nasal septum, hypertrophic turbinates or an improperly working nasal valve. Polyps may block the nasal passage and hence lengthen the duration of rhinosinusitis or render a secondary infection by bacteria more likely. Although concha bullosa frequently occurs, most researchers do not believe that it is a risk factor for rhinosinusitis [29]. Despite this relative consensus, it has sometimes been reported [30] that chronic sinusitis is more common in cases featuring concha bullosa, but causality is not certain in these individuals.

44.4.6 Rhinitis Secondary to Physical or Chemical Irritation

Where rhinitis is secondary to physical or chemical irritation, it is treated by elimination of the trigger, ensuring the environment is better ventilated, installing air filters and occasionally wearing a mask. Rhinitis medicamentosa happens with chronic usage of topical nasal decongestant preparations and can be rectified by stopping use of the medication [17].

44.4.7 Occupational Rhinitis

Occupational rhinitis needs inclusion in the differential diagnosis in cases of UACS, whatever the nature of the triggering substance. The clinician should suspect occupational rhinitis if a relationship is established between symptomatic deterioration and a working environment. Occupational exposure may have caused the problem or may worsen an existing condition.

Symptoms of occupational rhinitis (both atopic and non-atopic kinds) are sneeze, nasal discharge and blocked nose.

44.4.8 Rhinitis Medicamentosa

Rhinitis medicamentosa is a disorder wherein the chronic use of nasal decongestants, which promote mucosal vasoconstriction, paradoxically causes nasal blockage. Whilst often secondary to topical decongestants, such as oxymetazoline hydrochloride, snorting cocaine can also produce the same problem. Nasal decongestants stimulate adrenergic receptors to cause vasoconstriction, but in the longer term, the parasympathetic system adjusts the balance, resulting in nasal swelling and blockage. Beta-blockers may also be responsible for blocked nose.

44.4.9 Pregnancy Rhinitis

Pregnancy rhinitis is non-specific and occurs in expectant mothers, but not after birth. The disorder is transient but may cause distress to the patient and her relatives, particularly if coughing is very marked.

44.5 Treatment

Treating UACS depends on the underlying cause. Where no particular diagnosis appears to explain the phenomenon, treating empirically is a reasonable course of action.

The particular treatments for each disorder are outlined below. The main themes to consider in treatment are:

- Avoiding triggers
- Anti-inflammatory therapy to reduce inflammation and hypersecretion
- Treating infections
- Rectifying anatomical anomalies

44.5.1 UACS Secondary to Allergic Rhinitis

The first-line therapy for UACS secondary to allergic rhinitis typically consists of intranasal steroids and antihistamines, with or without decongestant [31]. Following on from multiple RCTs involving treatment of AR [32–37], abundant evidence exists for the efficacy of intranasal steroids, nasal cromolyn, topical antihistamines, systemic leukotriene receptor antagonists and systemic antihistamines in treating AR-associated coughing. Antihistamines that produce little sedation are more effective in AR than in nonallergic rhinitis. In the latter case, anticholinergic activity by older antihistamines seems to be a key factor in their efficacy [38]. Treating AR with a combination of an antihistamine and decongestant has been usual practice for a long time and is frequently effective [36]. Leukotriene receptor antagonists also possess demonstrable efficacy in alleviating AR symptomatology [37].

A key element in successful management is avoidance of the trigger. Allergen immunotherapeutic desensitisation may be beneficial in the longer term.

44.5.2 Vasomotor Rhinitis

Sedating antihistamines typically possess efficacy in treating vasomotor rhinitis, thanks to their anti-cholinergic activity. Ipratropium bromide intranasal spray potentially offers benefit in AR. However, the evidence for benefit is confined to one prospective trial with low numbers of participants [18]. That trial indicated a role for ipratropium bromide where the combination of antihistamine and decongestant lacked efficacy or where a contraindication existed, such as glaucoma or benign prostatic hypertrophy with symptoms.

44.5.3 Postviral Upper Respiratory Infection

Postviral cough can persist for some 8 weeks and is often reduced by a salbutamol inhaler.

There is a single double-blind RCT with placebo control which evaluated combined antihistamine and decongestant in patients with acute coughing, where the efficacy was consistently high [39].

There have also been low-quality prospective descriptive trials in persistent cough [18, 40, 41]. These trials used dexbrompheniramine maleate (6 mg twice daily) or azatadine maleate (1 mg twice daily) with enteric-coated pseudoephedrine sulphate (120 mg twice daily). However, trials of newer, less sedating antihistamines (terfenadine in two trials [42, 43] and loratadine with pseudoephedrine in one trial [44]) in suppressing acute coughing in coryza did not find these agents were efficacious. Since first-generation antihistamines are no longer recommended because of their sedative properties and propensity to cause cardiac arrhythmias, an alternative would be to try inhaled ipratropium or salbutamol. [45]

44.5.4 Rhinosinusitis

Acute bacterial rhinosinusitis is most frequently the result of infection with *Streptococcus pneumoniae* and *Haemophilus influenzae*. A range of other bacterial pathogens may also be responsible, such as anaerobic species, streptococci, *Moraxella catarrhalis* (particularly in paediatric cases) and *Staphylococcus aureus*. The pharmacological management of acute bacterial sinusitis involves antimicrobials, nasal steroids to dampen inflammatory responses and nasal decongestant agents, e.g. oxymetazoline hydrochloride. Antibiotic agents include amoxicillin, co-amoxiclav, second- or third-generation cephalosporins (cefuroxime axetil, cefprozil, cefixime), macrolides (clarithromycin, azithromycin) and the quinolones (levofloxacin, gatifloxacin, moxifloxacin).

Even though nasal steroids have demonstrated benefit [46], RCTs that are prospective and double-blind do not exist to demonstrate that decongestant therapy (topical or systemic) possesses efficacy in sinusitis, whether acute or chronic.

It is yet more unclear how best to manage chronic rhinosinusitis (CRSsNPs). What role bacterial infection plays in this disorder and how helpful it is to initiate antibiotics remain subject to debate. Results from four studies of a prospective and descriptive design [18, 40, 41, 47] have nonetheless shown efficacy from the following medication regimens: at least 3-week duration of an antibiotic with activity against *H. influenzae*, anaerobic oral bacteria and *S. pneumoniae*; no less than 21 days' course of first-generation antihistamine plus nasal decongestant; and 5-day course of topical decongestant b.d. After coughing stops, steroids should still be administered to the nose for a further 3 months. In cases where there is a laboratory-proven persistent infection of the sinus which fails to respond to antibiotic therapy and an anatomical anomaly is obstructing the airway that can be addressed via endoscopic sinus surgery, endoscopic surgery may be an option.

Management of allergic fungal sinusitis usually entails operative removal of the allergic fungal mucin, followed by allowing air into the sinus and ensuring it can drain efficiently [48]. Steroids serve only to dampen the allergic response. There is potential advantage in administering systemic antifungal therapy prior to surgery, but this is a topic which has not yet been thoroughly investigated in the literature.

44.5.5 Rhinitis Secondary to Physical or Chemical Irritation (Including Exposure Through Work)

If an irritant substance responsible for rhinitis is evident, the following steps are efficacious in managing the condition: avoid exposure, ventilate the area thoroughly before working, use an air filter, and, in exceptional cases, use personal protective equipment such as breathing masks with a high level of capacity to remove particulate matter in industrial settings.

44.5.6 Rhinitis Medicamentosa

In rhinitis medicamentosa, the essential step is to halt or tail off usage of the decongestant. It may be defensible to recommend antihistamines and decongestants in combination, but this approach has not been systematically evaluated.

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Does Immunodeficiency Matter in ENT?

45

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45.1 Introduction

Primary immunodeficiencies (PID) are found in around 1 in 10,000 American children and 1 in 20,000 children in Europe. Given the difficulty in recognising the condition, clinicians need to be alert to the possibility of PID, if they are to identify it at an early stage. Groups representing both patients and their families have identified a 10-point checklist of warning signs showing PID. The signs include [1, 2]:

- At least four separate ear infections within 12 months.
- At least two grave sinusal infections within 12 months.
- Antibiotic treatment by mouth with a duration of 2 months minimum, with minimal benefit.
- Pneumonia at least twice within 12 months.
- An infant fails to achieve expected growth.
- A deep cutaneous abscess, or abscess within an organ, that recurs.
- Oral candidiasis that persists or mucocutaneous fungal infections.
- Only when antibiotics are given parenterally do they resolve infections.
- Firmly entrenched infection, e.g. septicaemia, on at least two occasions.
- PID in a genetic relative.

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_45

According to Subbarayan et al. [2], a history of PID in a relative, plus the necessity for antibiotic therapy to be intravenous, should be used as criteria to consider a specialist referral for possible PID.

45.2 Primary Immunodeficiencies

45.2.1 Humoral (Disorder Affecting B-Cells)

Seventy-Eight Percent of PID in the USA and 55% of European PID are of humoral type [3].

45.2.1.1 General Features

- Cases appear after the age of 3 months, since maternal antibodies do not persist after that point.
- Microorganisms with a capsule, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, produce repeated infections of the respiratory tract (ears, sinuses and lungs).

45.2.1.2 Lack of B-Cells (Agammaglobulinaemia)

X-linked agammaglobulinaemia (XLA) is responsible for 84% of European cases of agammaglobulinaemia. There is a defect in the Btk (Bruton tyrosine kinase) gene. Serological titres of IgG, IgA and IgM are very low. Physical examination of infants may indicate the absence of tonsils or lymph nodes. Such infants are prone to severe infection by bacteria with capsules. They may have persistent diarrhoea and chickenpox that recurs.

45.2.1.3 Reduced Numbers of B-Lymphocytes or Antibody Levels (Hypogammaglobulinaemia)

This disorder may present with a number of different features:

- IgA levels may be low. This accounts for 30% of cases in the USA and is the most frequent disorder to affect B-lymphocytes seen in the US.
- In 26% of cases (in the USA), a particular subclass of IgG is deficient: IgG2, IgG3 or IgG4.
- Common variable immunodeficiency (CVID) accounts for 15% of American cases and 46% of European hypogammaglobulinaemia. The onset has a bimodal distribution, the peaks being in the preschool age range and again in young adults. There are deficiencies in two isotypes and usually the total IgG level will be low. Whilst the features resemble XLA, the condition is less severe. Just as with other conditions where antibody function is impaired, infections of the ears, sinuses and lungs are expected. Diarrhoea results from infection with *Clostridium difficile* or microorganisms of the genera *Giardia*, *Salmonella*, *Campylobacter* or *Yersinia* and may cause malabsorption.

45.2.1.4 Transient Hypogammaglobulinaemia of Infancy

This condition accounts for 3% of American cases of PID. It is characterised by a higher than usual level of respiratory infections by bacteria, but these are of mild severity. The deficiency resolves spontaneously by the age of 2–4 years.

45.2.2 T-Cell Disorders

Disorders of T-lymphocytes represent 9–10% of PID in both American and European populations [3].

45.2.2.1 General Features

The majority of T-cell disorders involve both T- and B-lymphocytes, since they depend on each other to carry out their functions.

- **Severe combined immunodeficiency (SCID)**

  In this condition, severely impaired functioning of T-lymphocytes leads to derangement of B-lymphocytic function. The genetic basis is either X-linked or autosomal recessive. It occurs at a frequency of 1 in 100,000 live births within the USA. The condition appears before the child is 3 months old. The presenting features are diarrhoea, infections by opportunistic microorganisms, infections that are marked in severity and overall failure to thrive.

  If the diagnosis is made by the age of 3.5 months and stem cell transplantation occurs, 90% of such infants live. If this occurs later, the survival rate falls to 70%. For this reason, in the USA screening is being introduced. In 2013–2014, around 1/3 of US states had added the condition to their neonatal screening panels. 1.5% of babies born at term have a false positive on screening. Premature infants tested in intensive care have a 5% false-positive rate. Retesting is therefore needed in such cases.
- **Ataxia-telangiectasia**
- **Hyper-IgM syndrome**
- **Wiskott-Aldrich syndrome**

  Eczema-thrombocytopenia-immunodeficiency syndrome (Wiskott-Aldrich syndrome) displays X-linkage and is usually discovered when the patient is approximately 21 months old. The classic presentation has the triad of low platelet count, recurring middle ear infection and dermatitis. This only occurs 27% of the time, however. The thrombocytopenia leads to haematemesis, melaena and intracranial bleeds (potentially fatal) in up to 30% of cases.
- **DiGeorge syndrome (velocardiofacial)**

  This condition arises from the deletion of a section of chromosome at the 22q11.2 location, which leads to a hypoplastic thymus. A deficiency of T-cells becomes apparent through the patient developing severe viral infections, even from the administration of attenuated vaccines. Candidiasis lasts longer than a year. There is a low calcium due to hypoparathyroidism. The heart and face also have characteristic morphological anomalies.

45.2.3 Phagocytic Disorders

Phagocytic disorders represent between 8.5% (in the USA) and 12.5% (in Europe) of cases of PID.

45.2.3.1 General Features

The term encompasses conditions that affect either neutrophils or monocytes. Presenting features include pulmonary fungal infections, abscesses that keep recurring and slow-healing trauma. An invasive infection might be the initial presentation. Catalase-positive microorganisms (*Staphylococcus aureus*, *Pseudomonas* spp., *Aspergillus* spp., *Burkholderia cepacia*, *Nocardia* spp., *Serratia* spp., *Candida* spp.) may cause infections, especially if invasive.

- **Decreased absolute neutrophil count (ANC below 500/μL)**
  This may result from chemotherapy, or the neutropenia may be severe and congenital. In the latter case, it becomes evident within the weeks following birth. The umbilical stump may become infected. Neutropenia may also arise from autoimmune destruction or be cyclic.
- **Decreased neutrophil function**
  Decreased neutrophil function occurs in chronic granulomatous disease (CGD). This is an inherited disorder of NADPH oxidase that causes neutrophils to be unable to kill phagocytosed microorganisms. It is generally apparent by the age of 5 years. Umbilical stump infection may be the initial presentation. Recurrent pneumonial illness, abscess formation, suppurative adenitis and gut infections are also frequently seen.
- **Leukocyte adhesion deficiency (type 1)**
  This condition becomes apparent in early infancy. The umbilical cord is slow to separate and is still attached 4 weeks postnatally. Omphalitis and erosive ulcers in the perianal region may be apparent.
  Chediak-Higashi syndrome may also occur (see later).

45.3 Presentations of Immunodeficiency in ENT

The following are indications that a child patient is having an excessive number of infective episodes and therefore warrants a more detailed immunological review [4]:

- Antibiotic therapy is prescribed on more than four (if a child) or two (if an adult) occasions annually.
- Greater than four separate episodes of ear infection annually in a patient aged above 4 years.
- If the patient has had pneumonia twice.
- Sinusitis secondary to bacterial infection has happened more than three times within a year, or persistent sinusitis has developed.
- Prophylactic antibiotics have become necessary.

- A pattern of bacterial infection that is not age-appropriate.

Referral to an allergy or immunology specialist is always warranted if any of the following occur [2]:

- Rhinosinusitis becomes persistent or recurs.
- New presentations of an infection occur on more than eight occasions within 12 months.
- Sinus infection of a severe kind occurs twice in a year.
- Antibiotic therapy of at least 2 months' duration does not lead to improvement.
- Pneumonia occurs at least twice in 1 year.
- Failure to thrive in infants.
- Deep cutaneous or organ abscess formation occurs.
- Antibiotic therapy needs to be given intravenously.
- At least two infections are deep-seated.
- There is a family history of deficient immunity.

PID is fairly rare. Paediatric cases usually involve chronic or repeated infections by opportunistic microorganisms. The pattern of organ involvement means ENT specialists are likely to be consulted. Furthermore, sinusitis is a frequent presentation. For these reasons, a targetted surgical and medical approach is definitely warranted. As a first step, paediatric cases where infections keep returning needed to be worked up for potential immunodeficiency by examining cellular and humoral elements of the immune response [4].

With the exception of those immune disorders that present in very early life and are frequently life-threatening or fatal (such as SCID), the most frequently encountered immunodeficient conditions likely to be seen in ENT are agammaglobulinaemia and Btk deficiency disease (X-linked and autosomal recessive variants), IgA deficiency and hyper-IgE syndrome, common variable immunodeficiency (CVID), hyper-IgM syndrome, DiGeorge syndrome and ataxia-telangiectasia [4].

45.3.1 Impairments to Innate Immunity

45.3.1.1 Weakening of Anatomical Barriers

Cystic Fibrosis (CF)

The genetic defect that causes cystic fibrosis is mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene [5]. The protein produced by the gene regulates transportation of chloride ions across the external cell membrane and thus, indirectly, directs the movement of water [6]. CF is characterised by excessively viscous mucus production. This hyperviscosity means mucociliary clearance throughout the respiratory tract is impaired. CF sufferers are prone to repeated severe episodes of bronchiectasis, chronic rhinosinusitis and polyp formation in the

nose. The most common infective agents are *S. aureus* and *Pseudomonas aeruginosa* [4]. All children with nasal polyposis should be tested for cystic fibrosis.

Primary Ciliary Dyskinesia (PCD)

PCD may occur singly or as part of a syndrome, such as situs inversus viscerum or dextrocardia in Kartagener's syndrome. There are numerous single-gene mutations that can cause the condition, the majority of which are to do with dynein within the cilia. They result in reduced or absent movement by the cilia and hence mucociliary drainage problems [7]. Presentation with repeated otitis media with effusion with drainage occurring through the grommets should alert the ENT surgeon to the need to test for PCD.

Fortunately nasal levels of nitric oxide (nNO), an easily obtained measurement, are very low in PCD and are low in cystic fibrosis. nNO is sufficiently low in PCD to be used for screening, with an nNO level of >105 ppb giving a specificity of 88%, a sensitivity of 100% and a positive predictive value of 89% [8].

ENT specialists are often requested to biopsy the nose or the mucosal surface of the trachea to allow PCD to be definitively confirmed [4, 9].

45.3.2 Defects in Phagocytic Activity

45.3.2.1 Myeloperoxidase Deficiency (MPO)

The most frequently occurring congenital defect in neutrophilic activity is MPO. However, the majority of such cases have no symptoms because neutrophils in this condition still work through the oxidative killing pathways [4, 10].

45.3.2.2 Chronic Granulomatous Disease (CGD)

CGD results from numerous genetic mutations in the PHOX gene, responsible for the enzyme NADPH (nicotinamide adenine dinucleotide phosphate) oxidase. This enzyme allows oxygen radical species to be produced, which aid in killing bacterial and fungal invaders. Deficiency is of two types: quantitative and qualitative. How severe the resulting disease is linked to remaining expression of functional NADPH oxidase [4].

45.3.2.3 Chediak-Higashi Disease (CHD)

CHD is rare. It is characterised by numerous deficient physiological processes, including grossly deficient neutrophilic activity. The LYST gene is mutated. Normally this gene is involved in how intracellular vesicles fuse. Neutrophils have deficient chemotaxis and degranulation and their killing by granules is impaired [11]. Patients with CHD have repeated infections by bacteria such as *S. aureus* and beta-haemolytic streptococci. Reports indicate that cases may present with marked periodontitis, peripheral neuropathy, thrombocytic defects and learning disability [4].

45.3.2.4 Hyper-IgE Syndrome (HIgES)

HIgES is characterised phenotypically by changes in the chemotactic behaviour of neutrophils and monocytes [4].

45.3.3 Defects in the Complement Cascade

Defective composition of complement proteins (C2, C3, H, I, P) leads to the patient having repeated infections by bacteria with capsules. Since this predisposes sufferers to infection by *Neisseria meningitidis*, meningitis or septicaemia is a risk. Middle ear infections and sinusitis commonly occur and insertion of a grommet is typically indicated [12].

45.3.4 Defects Affecting Humoral Immune Mechanisms

45.3.4.1 Transient Hypogammaglobulinaemia of Infancy (THI)

Between the ages of 3 and 6 months, there is a usual decrease in IgG levels, but this decrease is exaggerated in THI. The level of IgM stays low until the child reaches the age of 1 year and is normal by age 2 or 3 [13]. Although children often have no symptoms from THI, some do suffer from repeated infections of the upper or lower airway and associated organs. Acute middle ear infection may occur. It is rare for severe illness to happen, however [4].

45.3.4.2 X-Linked (Bruton's) Agammaglobulinaemia (XLA)

In XLA, B cells and plasma cells are entirely absent. Due to maternal immunoglobulins being present up to the age of 6 months, symptoms do not usually appear until after that age. After the age of 6 months, pyogenic bacterial infections occur repeatedly. The causative organisms are *P. aeruginosa*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and other *Streptococcus* species. Most cases have rhinosinusitis as their presenting complaint when seen in ENT [4].

Treatment for XLA involves infusing replacement immunoglobulins and making sure no live vaccines are used for any vaccinations [4].

45.3.4.3 Common Variable Immunodeficiency (CVID)

The clinical presentation of CVID resembles that of XLA, although the onset is usually later and the phenotype is less severe. Since CVID is not X-linked, the sex distribution is not skewed as in XLA [4].

45.3.4.4 Selective IgA Deficiency (IgAD)

IgA plays a key role in mucosal immunological defences. It is normally secreted into the gut and the respiratory tract. IgAD is the most frequent condition where immunoglobulin function is deficient [4].

45.3.4.5 IgG Subclass Deficiencies

IgG subclass deficiency occurs frequently and may present in various ways [14]. Although the total IgG level synthesised is at a normal level, a particular IgG isotype may be deficient, the most common isotype affected being IG2. Immunisation may fail to spur production of specific antibodies. The condition is sometimes found in connection with infections of the upper respiratory tract, especially middle ear and sinopulmonary disease [4].

45.3.4.6 Hyper-IgM Syndrome (HIgM)

In HIgM, the IgM titres may be normal or raised. It is usual for patients with HIgM to get repeated episodes of sinus and lung infections by bacteria from the age of 6 months onward. There may be a marked tendency to infection in the peritonsillar and other soft tissue regions [15].

45.3.5 Cell-Mediated Immunodeficiencies

45.3.5.1 DiGeorge Syndrome (DGS)

The genetic mutations causing DGS are located at 22q11.2 (del22). This region codes for genes responsible for the third and fourth pharyngeal clefts and their associated structures, such as the parathyroid glands and the thymus. There are several variants in the deficiency caused. The thymus is a retrosternal organ with a key part to play in immune development and functioning [16]. It is here that T-cells undergo maturation. The deficient thymus means that DGS sufferers have a severe lack of cell-mediated immune responses and thus have repeated severe infective episodes [4].

45.3.5.2 Chronic Mucocutaneous Candidiasis (CMC)

CMC produces repeated infection by *Candida* of the skin, nails, mucosal surfaces and upper portion of the gut [17]. The diagnosis depends on the appearances at physical examination, the KOH test, mycological culture and an account of repeated candidal infections that resist treatment [4].

45.4 Secondary Immunodeficiencies Presenting to ENT

Secondary immunodeficiencies are more frequently encountered than primary immune dysfunctions, which are, in fact, determined by genetic abnormalities of the immune system.

45.4.1 Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)

HIV represents several retroviruses, which can damage immune function, hindering the immune system's ability to fight off infection or neoplasia. The pattern of

damage involves injury to both humoral and cell-mediated immune mechanisms. Damage to cellular-mediated immunity exposes the patient to infection by *Pneumocystis jirovecii* organisms and viruses, whilst humoral system injury increases the risk of repeated infection by bacteria. Thus, repeated middle ear infections, sinusitis, cutaneous and soft tissue infection, urinary tract infection, pneumonia and septicaemia are more common in HIV patients [4].

ENT presentations by HIV patients are very frequent. Indeed, 40% of sufferers have an ENT-related problem. In children, HIV most often presents as a mucocutaneous infection, i.e. oral candidal infection. There are reports of HIV presenting with oesophageal candidal infections, but these are less frequent. The presenting complaints may be painful swallowing and failure to thrive, especially up to and including in toddlerhood. Signs seen in the mouth include herpetic lesions on the mucosal surfaces and petechiae on the palate, resulting from a platelet deficiency. Repeated middle ear infections are common in children with HIV. The causative agents are *Staphylococcus epidermidis*, *S. pneumoniae*, enterococci, *Escherichia coli* and *Pseudomonas aeruginosa* [17]. It is advisable to instigate treatment aggressively, and grommet placement, as well as pressure equalisation tubes on both sides, may be needed early on. This is likely to be the case in around 60–75% of children with HIV who have symptoms [4, 18, 19].

45.4.2 Radiotherapy

Tumours appear inside a microenvironment, formed by the cells of the normal immune system, which can determine either tumoral suppression or progression. Radiotherapy is the most frequently used treatment in cancers, especially in solid tumours, with a rate of 60% indication either curative or palliative [20, 21]. The general effects of the radiation are observed in the entire microenvironment from which the tumours arise.

The radiosensitivity of the tumour is elevated especially in case of presence of the lymphocytes (type T-, type B- or type NK-cells), monocytes or the macrophages cells. The antigen-presenting cells (dendritic cells) have proven an increased radioresistance [22].

Patients undergoing radiotherapy for malignancies of the head and neck, in particular, are at risk of developing severe lesions of radiodermatitis and radiation-induced mucositis, which contribute to local and systemic infections with bacteria, yeast and viruses. The studies indicate [23, 24] important oral mucositis, which appeared in 29–66% of the patients who received radiation therapy for cancers of the head and neck. Oral candidosis, dysgeusia, dysphagia, osteoradionecrosis, necrosis of the soft tissues, trismus and xerostomia represent a part of the complications of radiotherapy, which affect the quality of life of the patients involved and determine a prolonged recovery period.

45.4.3 Hematologic Malignancies

In case of hematologic neoplasia, the acquired infections represent the main cause for the morbidity and mortality, especially in patients with multiple myeloma, chronic lymphocytic leukaemia, Hodgkin or non-Hodgkin lymphoma. The development of new therapeutic strategies had an effect on the duration of the disease remission, but the presence of relapses with palliative therapy is able to determine prolonged suppression of the immune system and, consequently, a higher risk of systemic and local infections.

The immunodeficiency in hematologic malignancies has a plurifactorial aetiology, related either to the disease itself or the treatment (chemotherapy, corticosteroids, immunosuppressants, monoclonal antibodies, radiotherapy or bone marrow transplant). Invasive fungal rhinosinusitis (*Aspergillus* spp., *Mucor* spp., *Fusarium*) is one of the most frequent complications in patient with immunocompromising diseases.

45.4.4 Anti-Inflammatory and Immunosuppressive Medical Therapy

In chronic inflammatory diseases, such as autoimmune affections, allergic conditions or transplantation rejection, it is indicated to use substances, which are able to modulate the immune response. The drugs with an effect of suppression of the immune system can be classified into biologic therapy, corticosteroids, inhibitors of calcineurin and cytotoxic substances. The most important side effect of these medicines is that they induce a weakening of the patients' immune response, who become susceptible to infections of multiple aetiologies (viral, bacterial or fungal).

45.4.4.1 Biologic Therapies

Biologic drug therapy (T- and B-cells monoclonal antibodies, antithymocyte globulins) is not usually characterised by immunosuppression, but they prove different side effects, which can impair the patients' immune defence, with the occurrence of severe infections or the appearance of autoimmune conditions or malignancies [25–27].

45.4.4.2 Corticosteroids

Glucocorticosteroids are frequently used, especially in ENT practice, to reduce an excessive inflammatory response, which produces tissue damage. The cellular effects of corticosteroids are a decrease of cytokine production (interleukin-1, interleukin-6 and TNF-α), leukocytes chemotaxis, cellular adhesion and phagocytosis. Due to the pro-apoptotic effect and the inhibition of proliferative responses through interleukin type 2, lymphopenia occurs during the treatment [26]. The effects on the immune system increase susceptibility to viral, bacterial or fungal infections, depending on the dose and duration of the treatment. During steroid treatment, there are several possible complications such as oral candidiasis (frequently encountered

in inhaled steroid use) or herpes zoster which often appear in patients with chronic administration of systemic glucocorticosteroids.

45.4.4.3 Calcineurin Inhibitors

Calcineurin inhibitors, such as cyclosporine, tacrolimus and sirolimus, have the ability of binding cytoplasmic proteins, which belong to the immunophilin family, and inhibiting the interaction with calcineurin. This interaction is essential to activate IL-2 transcription and T-cell normal function [27]. Compared to corticosteroids and cytotoxic drug therapy, they do not interfere with macrophage and neutrophil function, so they do not increase susceptibility to local or general infections. It has been observed, however, that these medicines cause infections of the respiratory tract and of the skin, usually with viral aetiology. Among their side effects, an increased incidence of lymphoproliferative diseases and cutaneous neoplasias is noted.

45.4.4.4 Cytotoxic Agents

Cytotoxic drugs (cyclophosphamide, methotrexate, mycophenolate, azathioprine, mercaptopurine, sulfasalazine or hydroxychloroquine) were first developed to control tumour cells growth and to inhibit the bone marrow in case of transplantation, but their use has been extended to the treatment of autoimmune or inflammatory diseases, e.g. prevention of graft rejection [28]. They inhibit B and T proliferation and the consequent immune responses.

The major side effect of the drugs is the toxicity to hematopoietic and non-hematopoietic cells, with the development of cytopenias and gastrointestinal mucosal and skin lesions. The cytopenia may contribute to secondary immunodeficiencies and infection susceptibility.

45.4.5 Traumatic Causes

Traumatic and iatrogenic lesions determine discontinuation of the superficial epithelial layer and stimulate the proinflammatory response, with the production of cytokines IL-6 and TNF-α [29]. The risk of secondary infections, especially with *Streptococcus pneumoniae*, is greater in patients who underwent splenectomy.

45.4.6 Metabolic Diseases

Several metabolic diseases (diabetes mellitus, chronic kidney or liver disease) induce a state of deficiency of the immune system. Patients with diabetes mellitus present a poor lymphoproliferative reaction, due to hyperglycaemia (chronic multi-organic suffering), and they consequently develop cutaneous and respiratory infections with fungi, bacteria or viruses [30].

These patients tend to have a higher incidence and severity of acquired infections, as well as prolonged recovery time, compared to the healthy population.

45.5 Conclusion

During his or her working life, the average ENT surgeon will encounter patients with immunodeficiency, probably mostly secondary, but a few with primary causes, especially of those of innate immunity in children. Early recognition, accurate diagnosis and therapy can improve the prognosis for a healthy life for the sufferer in some of these conditions—so a level of alertness and awareness is necessary.

More subtle immune defects, such as an IgG subclass deficiency, one copy of a cystic fibrosis gene or a lack of bitter taste receptors, may underlie CRS without NPs in some patients [31].

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Is an Ideal Nasal Drop Able to Reduce All Symptoms of Allergic Rhinitis?

46

Ceyhun Aksakal, Görkem Eskiizmir, and Cemal Cingi

46.1 Introduction

Allergic rhinitis (AR) is a condition affecting the lining of the nose, featuring inflammation that occurs via IgE-linked mechanisms. At the early stage, the major symptoms are sternutation, rubbing the nose, runny nose, and tearing. Later on, the nose becomes blocked and cough may also accompany [1].

Trauma or inflammation within tissues may lead to the release of inflammatory signaling molecules such as the cytokines C5a and eotaxin, which promote chemotactic and inflammatory cell migratory responses [2]. This cytokine release is followed by a swift alteration in the adhesive tendency of the vascular endothelium, resulting in the pavementing of circulating leucocytes. A key stage in the development of this type of inflammation is the attraction of eosinophils into the tissue from the circulation [3]. The chemoattraction of neutrophils can be inhibited by trans-resveratrol [4].

In the majority of cases, AR has its onset in children or adolescents, with the cardinal symptomatology of repeated sneezing, nasal pruritus, discharge, and a blocked nose. The customary way to classify AR is into seasonal and perennial variants, reflecting the allergenic underpinning of the disorder, but the World Health

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_46

Organisation (WHO), in its Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, employs a classification scheme dividing AR into intermittent or persistent types, based on the symptomatic duration [5–8].

The usual sources of allergens implicated in AR are house dust mites; pollen from grass, trees, or weeds; mold; cats; and dogs [9]. It appears that some sufferers at least may have the symptoms of AR without having undergone allergic sensitization, the symptoms being produced by localized IgE production only. Such a situation is termed "entopy"—see Chap. 8 [10, 11].

46.1.1 What Is Known About This Topic?

- AR involves inflammation initiated through IgE occurring within the nasal mucosa.
- The symptoms fall into two phases: early-phase symptoms are sneezing, nasal pruritus, discharge, and tearing; late-phase symptoms involve blockage of the nose and, occasionally, coughing.

46.1.2 What Additional Benefit Could a Newly Formulated Nasal Drop Offer?

The current treatment modalities for AR are nasal steroids, nasal decongestants, anticholinergics, antihistamines, and panthenol. A novel pharmaceutical formulation that provides all the effects of the abovementioned drugs may be unique and has significant benefits such as single drug usage, cost-effectiveness, lesser side effects, etc.

46.1.3 Rationale for the Combination

The proposed ideal nasal drop would include the following:

1. A nasal steroid: mometasone furoate
2. A nasal decongestant: xylometazoline hydrochloride
3. An anticholinergic: ipratropium
4. An antihistamine: desloratadine
5. Panthenol

The proposed formulation enables to combine the anti-inflammatory, antihistaminic, decongestant, anticholinergic, and hydrating effects of these drugs into a single medicine.

46.2 Prevalence and Epidemiology of Allergic Rhinitis

AR is the most prevalent long-term disorder in childhood. Its peak occurrence is in children at school age [12]. The prevalence at ages 6–7 years is 15%, increasing to 40% at age 13–14 years. While AR has a male predilection in children, males and females are equally affected as adults [13]. Around 80% of all cases of AR have their onset before the age of 20 years, with concurrent allergic conjunctivitis (AC), giving eye symptoms, being a common comorbidity [14].

46.3 Pathophysiology

The most frequent type of rhinitis other than sinonasal infections is AR. It involves an IgE-linked immunological response to allergens [15]. The usual sources of allergens implicated in AR are house dust mites; pollen from grass, trees, or weeds; mold; cats; and dogs [16]. If there is no convincing evidence that the response is systemic, it is possible that a localized entopic response may be responsible for the symptoms [17]. IgE synthesized following prior sensitization has specificity for a unique antigen and coats the membrane of mast cells. When the allergic trigger is re-encountered, cross-linkage of IgE occurs, which provokes mast cells to degranulate, thereby releasing a range of pro-inflammatory mediators, notably histamine. Histamine plays a well-established part in the pathogenesis of allergy [18]. Histamine interacts with its receptors, labeled H1 to H4. Histaminergic action in allergic responses occurs through H1 binding, leading to smooth muscle contraction, spasm of the bronchi, greater leakiness of capillaries, and activation of sensory nerves and cough-related receptors [19].

Nasal symptoms (sneezing, pruritus, discharge) arise due to IgE-linked mast cell degranulation. In 65% of cases, the nasal mucosa is infiltrated by eosinophils, basophils, and T-lymphocytes responsible for synthesizing IL-4 (promotes IgE production) and IL-5 (promotes eosinophil increase). Given that antihistamines do not reduce congestion in the nose, it is reasonable to suppose that other signaling molecules play a role, e.g., prostaglandin D2 or the leukotrienes. The late phase of inflammation, with accompanying cellular infiltration of the mucosa, is also significant [20]. Recently, further elements of the pathophysiology of AR have begun to be known about, such as the role of H4 receptors, which antihistamines do not act upon, and the failure of Treg (T regulatory) lymphocytes to dampen down allergic responsivity [21]. Alongside the environmental influences on AR, it has become apparent from studying monozygotic and dizygotic twins that the disorder has a genetic component, albeit the precise genetic basis has yet to be determined [22].

46.4 Comorbidity

Children with AR frequently have comorbid conditions, and together these can have decidedly negative effects on the patient and family [23, 24]. Regardless of age, allergic dermatitis and rhinitis are commonly found comorbidly [25]. Medical complications in children with AR frequently include several diseases such as otitis media with effusion (OME), persistent or recurrent sinusitis, and asthma. The psychosocial sequelae are impaired sleep, diminished academic achievement, hyperactive behavior, and overall lower quality of life [5].

46.4.1 Asthma

Epidemiological studies have demonstrated a powerful association between AR and asthma, found in nearly all asthmatic patients. According to Wright et al., if an infant has the diagnosis of AR, the risk of asthma is increased dramatically as the child becomes 11 years old [26]. Among children suffering from rhinitis, 32% went on to become asthmatic, and a mere 5% of those with asthma had no evidence of rhinitis. Settipane et al. [27] performed a seminal study in which they followed up 1836 first-year students at Brown University for 23 years. The study had a prospective methodology and involved survey administration, interviews, physical examination, and skin prick testing to detect asthma or AR. At the 23-year mark, 64% of the original subjects (1021 individuals) sent back a filled-out survey. Some 72% of final respondents had undergone prick testing as first-year university students. The researchers concluded that having AR or being positive on prick testing meant an elevated risk of developing asthma in the future. First-year students with AR had a threefold increase in the risk of becoming asthmatic compared to their non-atopic peers [27]. The large, community-based longitudinal cohort study undertaken by Guerra et al. [28] examined how far rhinitis (both AR and NAR) independently raises the risk of developing asthma as an adult. Both AR and NAR significantly raised the risk of becoming asthmatic (crude odds ratio, 4.13; 95% confidence interval, 2.88–5.92). Individuals who had chronic or marked rhinitis symptoms affecting the nose and gave a history of clinically confirmed sinusitis were at even higher risk of becoming asthmatic. It is common in children for AR to occur before the onset of asthma, a situation referred to as “the atopic march.” Recent studies in which the effectivity of allergic immunotherapy in children with AR was evaluated demonstrate that such treatments may decrease the risk of asthma in adolescents. An open-label study involving 113 pediatric patients with AR secondary to grass pollen but no other allergic responses of clinical significance, who were allocated at random to either specific sublingual immunotherapy over 3 years or standard treatment of symptoms, was carried out by Novembre et al. [29]. Subjects who received immunotherapy had a 3.8-fold decrease in their subsequent risk of becoming asthmatic than those on standard treatment. A study by Niggemann et al. in which pediatric patients with AR secondary to grass or birch pollen followed for 5 years after a 3-year course of specific subcutaneous immunotherapy was also published [30].

46.4.2 Otitis Media with Effusion

Otitis media with effusion (OME), a major health problem worldwide, affects more than 80% of children at least once. Approximately 40% of children suffer from OME at least three times by the age of 3 years [31]. Tomonaga and colleagues compared the rate of OME in pediatric patients with AR and healthy children. They found a rate of 21% in pediatric patients with AR and 6% in healthy children. Caffarelli et al. [32] demonstrated that AR symptoms in children and OME were significantly associated and proposed that AR is significant in the way OME develops. Similarly, Chantzi et al. [33] identified IgE-linked hypersensitivity and blockage of the nose as independent determinants of risk for pediatric OME. In experimental studies, Skoner et al. [34, 35] demonstrated the dysfunction of the eustachian tubes induced by placing allergens or substances that mediate allergy within the nose. A survey by the PAA gave the result that otalgia due to the pressure was fivefold more common in pediatric patients with AR in the month when their allergic symptoms peaked, and the risk of undergoing a surgical procedure (myringotomy tube insertion and adenoidectomy and/or tonsillectomy) doubled, compared to non-diseased children of the same age [36]. According to Nguyen et al., the levels of T-helper 2 cells in effusions of the middle ear elevated in pediatric patients with AR, indicating that allergic processes play a role in OME [37]. Briefly, these findings point to the involvement of AR in the pathogenesis of OME. Thus, it is reasonable to evaluate AR when considering pediatric patients with OME.

46.4.3 Rhinosinusitis

Rhinitis and sinusitis may be linked by spread from one anatomical compartment to another, thereby setting up a similar inflammatory response, as occurs when rhinitis causes the osteomeatal complex to become obstructed. On the other hand, the situation may represent different manifestations of the same underlying pathology, i.e., allergy [38]. A group of 70 pediatric patients with AR from Los Angeles, with an age range of 3–16 years, were examined radiologically: 53% had abnormal appearances of the sinus, consisting of notable thickening of the walls of the maxillary sinus in 6% (4 individuals) and with at least 1 sinus totally opacified in 21% (15 individuals) [39].

Allergic rhinitis may lead to grave sinus-related complications in children. Acute rhinosinusitis in a child may lead to complications affecting the orbit, a process in which AR acts as a risk factor, as Holzmann reported [40]. A total of 102 pediatric patients with edema affecting the orbit are imaged using computerized tomographic scanning of the paranasal sinuses and signs of AR investigated. In 60 children (58.8%), the orbital pathology was secondary to acute rhinosinusitis, as observed clinically or by imaging. For those cases where preseptal cellulitis was present (14 individuals), 64.3% (9 children) had signs of AR. Allergic rhinitis was also present in 25% of those with periostitis (1 child out of 4) and 76.5% (13 out of 17) of cases with subperiosteal abscess. Based on these findings, the authors advocated that AR might be significant in the way acute rhinosinusitis can affect the orbit.

46.5 Pharmacological Treatment

46.5.1 Oral or Intranasal Antihistamines

The main pharmacological agents used to treat AR are antihistamines or intranasal corticosteroids. Antihistamines are available as both topical and oral preparations. Their efficacy is greatest when treating symptoms found early in AR. Antihistamines of the second generation possess efficacy whether given orally or topically, and patients usually tolerate them well, albeit sedation is a recognized side effect [41]. Cetirizine, fexofenadine, loratadine, desloratadine, and levocetirizine all belong to the second generation of antihistamines and are available as oral preparations. They do not require prescription apart from desloratadine. Antihistamines that are given by nasal spray require a prescription—azelastine and olopatadine. Antihistamines from the first generation are not suitable treatments as their therapeutic index is unsuitable [42–45].

Second-generation antihistamines possess equivalent efficacy, regardless of the route of administration [46–52]. The oral route is associated with higher tolerability, but topical treatments begin working more immediately [45]. For a small number of children, even second-generation antihistamines are sedating [53]. Fexofenadine may be superior in this regard [44].

46.5.2 Intranasal Corticosteroids

Meta-analysis showed the highest efficacy possessed by intranasal corticosteroids (INCs) [50–53]. They have equal or superior efficacy to combined treatment with an antihistamine and a leukotriene antagonist [54]. A review by the Cochrane collaboration stated that INCs have little supporting evidence for their efficacy. This conclusion was, however, based on the exclusion of several RCTs of high quality, because they permitted rescue medications to be used. Some studies indicated that INCs have their onset of therapeutic benefit less than 4 h after the application of the first dose [55]. It is also claimed that INCs offer benefits in comorbid conjunctivitis [45, 56, 57], asthma, and hypersensitivity of the bronchi [53, 58–61]. Moreover, the tolerability of INCs is usually high. The more recent entrants to the market, such as fluticasone propionate [62], mometasone [63], and fluticasone furoate, are once-daily preparations. They are better therapeutic choices since they do not result in lower growth velocity over 12 months of therapy, unlike earlier products, e.g., beclomethasone and budesonide [64].

Intranasal corticosteroids inhibit inflammation in AR. Their use in adolescents or children aged 2 years or older is supported by numerous studies of high methodological quality [65–79]. As indicated above, the Cochrane review cites poor evidence for their use; however this depends on excluding trials permitting rescue medication [80]. Several clinical trials confirm that mometasone, fluticasone, and ciclesonide have their onset of therapeutic activity less than 1 day after the first dose [81]. There is evidence to suggest INCs are efficacious in comorbid asthma [82–84]

and that fluticasone furoate and mometasone affect conjunctivitis [65, 70, 85]. The better tolerability of the newer agents [70, 86–89] and their lessened effect on growth velocity [90, 91] are thought to be related to considerably lower bioavailability than the older products. While septal perforation and epistaxis listed as potential adverse effects of INCs, the literature does not offer any systematic investigation of their incidence [5].

46.5.3 Systemic Corticosteroids

It is not usual to employ oral steroids to treat children with AR, given that there exist several other effective treatment modalities with superior safety characteristics. In adults, though, the use of systemic steroids has been investigated and a 30 mg daily dose has been found to possess efficacy [92]. Since injected steroids may lead to localized muscular and skin atrophy, a reduction in mineral content of bone, and inhibited growth, they are not recommended in children with AR [93]. If, as occasionally happens, a child with AR does require systemic steroid therapy, prednisolone p.o. at a dose of between 10 and 15 mg o.d. is generally adequate, with accompanying specialist opinion.

46.5.4 Oral Leukotriene Receptor Antagonist

Even though how montelukast affects the cellular infiltrates when administered topically to the nose has not been identified yet, they can alleviate the symptoms of AR. It is known that montelukast exerts its effects on neutrophils and macrophages; however other mechanisms may also have a key role [94]. Cysteinyl leukotrienes have been demonstrated to be part of how asthma develops, where they provoke excessive mucus secretion, render the capillaries leakier, increase cellular recruitment by cells of the immune system, and promote edema [95].

Two high-quality, but small-sized, studies involving children with AR (of seasonal and perennial type) indicated that montelukast possesses efficacy as sole treatment [96, 97], a result confirmed by two meta-analyses, where most of the data concerned adult patients [98, 99]. While anticholinergic agents possess efficacy in the management of watery rhinorrhea in older adults, they fail to control pruritus, sneezing, or nasal congestion [100]. These classes of agents are rarely administered to children.

46.5.5 Topical Nasal Decongestants

A short period of using topical nasal decongestants may have value in decreasing the nasal blockage. However, longer duration of treatment might increase the risk of rhinitis medicamentosa, a condition in which there is rebound edema of the nasal mucosa. [83].

46.6 Combined Therapies for Allergic Rhinitis

It has already been proven that a preparation consisting of azelastine and fluticasone possesses greater efficacy than either agent administered as monotherapy in seasonal AR [84]. The additional benefit obtained from such combination therapy holds out the promise of a truly "allergic march-halting" agent in the future; however, more research is required.

Montelukast, a leukotriene antagonist (LTRA), entered the market as an agent to use in asthma; however, it has also found employment in the treatment of AR. The literature offers several systematic reviews and meta-analyses of RCTs involving montelukast, mostly involving adults with hay fever. They emphasized that montelukast is slightly superior to placebo and has the same level of efficacy as antihistamines; however inferior efficacy when compared with topical steroids in terms of mitigating symptomatology and increasing quality of life [85, 101, 102]. A combination of an LTRA with an appropriate antihistaminic agent such as loratadine, cetirizine, or fexofenadine may supply significant advantages than a monotherapy [85, 88, 101]. An RCT in which pediatric patients of hay fever are enrolled demonstrated that montelukast provided considerable benefits symptomatically and reduced numbers of circulating eosinophils. Nonetheless, there was no effect of significance on eNO titers [103]. Apart from this single study, the remaining trials involving montelukast principally chose outcome measures based on subjective assessment of the severity of upper respiratory symptoms, rather than objective assessment tools for gauging the degree of coexistent asthma [85]. There is a paucity of high methodological quality RCTs involving several centers and focusing on pediatric cases of hay fever. One such study concluded that children administered montelukast during the allergic season showed no significant benefit in terms of FEV1 [104]. Given the small effect sizes observed, plus the lack of benefit on wheezing [89], it seems unlikely (although not explicitly excluded, since the hypothesis has not been formally tested) that montelukast will prevent children with AR from going on to be asthmatic.

46.7 The Authors Propose that a Newly Formulated Nasal Drop for AR Is Needed

The current treatment for AR includes nasal steroids, nasal decongestants, anticholinergics, antihistamines, and panthenol. We proposed that a novel formulation containing all five types of medication might allow the benefits to be achieved from the use of one medicine only. The following agents would comprise the drop:

- Nasal steroid: mometasone furoate
- Nasal decongestant: xylometazoline hydrochloride
- Anticholinergic: ipratropium
- Antihistamine: desloratadine
- Panthenol

46.8 What Is the Evidential Basis for the Proposed Pharmaceutical Formulation? What Is the Rationale for the Choice of These Five Active Ingredients?

46.8.1 Nasal Steroid: Mometasone Furoate

Indeed, steroids can inhibit inflammation of whatever cause [105]. Currently, INCs are the most potent agents in countering the inflammatory response in AR. Therefore, they have the highest efficacy for the treatment of AR. Although the majority of patients with AR benefit from INCs in terms of pruritus, sneezing, nasal discharge, and congestion, INCs are not effective on eye-related symptoms. The potential complications of steroids such as suppression of the adrenocortex, inhibition of growth, and alteration in bone physiology arise in long-term and dose-dependent use [91].

Mometasone furoate is a synthetic glucocorticoid steroid employed in treating nasal allergy. Cortisol or hydrocortisone are endogenous glucocorticoids, synthesized by the adrenal cortex. All glucocorticoids possess a powerful ability to inhibit inflammation. Topical and intranasal usage may provide a high local concentration in the mucosa to be achieved without significant systemic absorption, thereby avoiding/minimizing adverse effects. Mometasone furoate is licensed for symptomatic management of AR in patients aged at least 2 years. As well as controlling existing symptoms, the agent also helps prevent flare-ups of hay fever in patients aged at least 12 years. Mometasone furoate may also be used for the treatment of nasal polyposis [106].

The rationale for the inclusion of mometasone furoate is to damp down the inflammation underpinning AR.

46.8.2 Nasal Decongestant: Xylometazoline Hydrochloride

Topical decongestant agents mimic the action of the sympathetic nervous system, causing vasoconstriction within the turbinates. Thereby, they open up the airway and reduce the nasal blockage [107]. Eskiizmir et al. objectively demonstrated that topical decongestant agents (oxymetazoline and xylometazoline) are fast-acting drugs that significantly decrease nasal resistance and increase nasal airflow [108]. Moreover, agents used in AR modulate autonomic regulation of the lining of the nose and reduce secretory activity. Vasoconstriction can be achieved via blockade of alpha-adrenoceptors, resulting in lower levels of vascular engorgement, and the antagonistic action at muscarinic receptors leads to a decrease in rhinorrhea [89].

The aim of including xylometazoline hydrochloride is to promote constriction of nasal blood vessels and thereby reduce nasal blockage. The watery rhinorrhea associated with AR may also decrease. As described earlier, sinusitis frequently coexists with AR. Decongestant agents are also of benefit in rhinosinusitis.

46.8.3 Anticholinergics: Ipratropium

Ipratropium antagonizes cholinergic transmission in both the bronchi and nasal passages. Both COPD and asthma cause airway constriction through cholinergic action on the smooth muscle of the airways. Ipratropium has an anticholinergic action, promoting smooth muscle relaxation and bronchial dilatation. Glandular mucus secretion is also under cholinergic control. The anticholinergic effect of ipratropium on mucous glands is of benefit in both AR and coryza. Thus ipratropium is indicated for symptomatic relief in rhinitis of both allergic and nonallergic type and the relief of nasal inflammation in coryza [109]. The rationale for adding ipratropium is to have an anticholinergic effect and diminish secretory activity in AR.

46.8.4 Antihistamine: Desloratadine

Recently, second-generation antihistaminic agents popularized as they are as efficacious as first-generation antihistaminic agents. Moreover, they are safer and have less toxic effects on the heart, sedation, and interference with psychomotor functioning [110]. The second-generation antihistaminic agents were designed to have greater specificity for the H1 histamine receptor [111] and thus fewer side effects. They offer clinical benefits in the symptomatic management of the early phase of AR, notably nasal discharge, itching, and sneezing. They are not of benefit in managing a blocked nose, which occurs in the late phase of AR. This ability to control both early- and late-phase symptoms of AR is the reason to combine an antihistaminic agent with a decongestant [99].

Desloratadine is a good example of antihistaminic agents. It acts by inhibiting histaminergic action, thereby able to reduce the symptoms associated with allergies such as sneezing, rhinorrhea, ocular pruritus, tearing, and pruritus and skin exanthems due to chronic urticaria [112]. Desloratadine, a second-generation antihistaminic agent, is suggested as the treatment of choice in AR with decongestant properties that have been proven in the literature [113–115]. Antihistamine therapy helps to reduce excessive secretory activity in AR. The rationale for including desloratadine is to exert an antihistaminic effect and lessen secretory activity in AR.

46.8.5 Panthenol

Panthenol (otherwise known as pantothenol), a provitamin of vitamin B5 (pantothenic acid), is rapidly oxidized in vivo to pantothenate. Panthenol is a liquid that possesses high viscosity at room temperature and is translucent and colorless. Pantothenic acid forms salts in powder form, usually (e.g., sodium pantothenate) white-colored. These salts dissolve in water, alcohol, propylene glycol, ether, and chloroform. Pantothenic acid salts are partially soluble in glycerin [102]. Panthenol is a hydrating agent that decreases pruritus and dermal inflammation and the epidermis heals more rapidly when it is applied [116]. Skin integrity is thus better

supported [117]. D-Panthenol is also found in nasal gels to diminish crust formation and pain after endonasal surgical procedures [110]. The rationale for including panthenol is to hydrate the nasal mucosa and lessen pruritus and inflammation in AR.

Editor's Comment

There are significant problems with this proposed multidrug drop. The first is formulation since the constituents may be incompatible or unobtainable in a form suited to nasal use. They may interact with each other once mixed in a liquid. The second is tolerization: the use of a steroid/decongestant combination is no more effective than corticosteroid alone after a few days. A decongestant and INCs combination (INCs-D) has already been considered for nasal congestion that is not improved by INS. Meta-analysis of six studies did not show benefits of topical decongestants addition to INCs [118]. Panthenol has been effective on skin, but the nasal mucosa differs from the epidermis. Thirdly if a reaction occurs to the medication, it will be difficult to assess to which drug or excipient it is directed.

In practice most AR sufferers are controlled by INS alone or an INS/INAH spray formulation. If more help is needed, additional medicines can be employed according to guidelines (see www.bsaci.org) or allergen-specific immunotherapy considered.

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The Threat from Emerging Virus Infections: Today and Tomorrow

47

Zerrin Özergin Coşkun, Cemal Cingi, and Sergei Karpischenko

47.1 Introduction

The title may have changed, but the situation is fundamentally the same as it was in 1960, as shown by the quotation above. Emerging viral infections continue to infect humans, some threaten human life today, but what about in the future? (Fig. 47.1).

47.2 Upper Respiratory Tract Infections

By its very nature as the passage by which air can enter the body, the upper respiratory tract is exposed to all manner of pathogens as well as polluting agents. Acute upper respiratory tract infection (URTI) refers to a transmissible infection of the upper respiratory tract, consisting of the nose, nasopharynx, pharynx, hypopharynx and larynx, and is a universal experience, despite decades of research.

The range of pathogens covers many viruses and bacteria. The common cold, caused by multiple different viruses, is the most familiar acute infective disorder affecting the upper airway, although other infections can also produce sinusitis, pharyngitis, epiglottitis and tracheobronchitis [2, 3].

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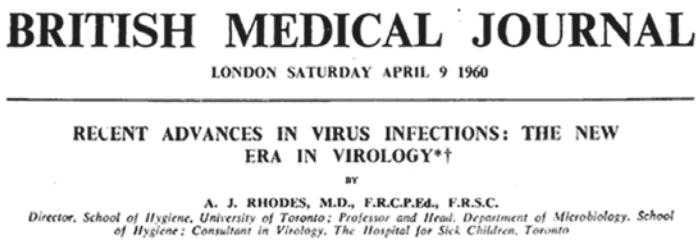
C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_47



BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 9 1960

RECENT ADVANCES IN VIRUS INFECTIONS: THE NEW ERA IN VIROLOGY*†

BY

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"This paper describes some of the advances in knowledge of virus infections of man, with particular reference to those new diseases discovered in the last few years, mainly by the use of improved technical methods. It may be claimed that virus diseases are now the most prevalent of the microbial infections of man, and by failure to respond to antibiotics they stand out in marked contrast to the bacterial infections. The only effective method of control of most of the virus diseases is prophylactic vaccination, and this method has already proved effective against some infections." (1)

Fig. 47.1 An unchanging picture for the last 60 years

47.3 Viruses

The term "virus" derives from Latin, where it refers to a poison [4]. It describes infective agent, too small to be visible on light microscopy, able to multiply only within the living cells of a host. A virus typically consists of a nucleic acid molecule (DNA or RNA) in a protein coat. It is estimated that the biosphere contains 10^{31} viruses and for every single human cell, 100 viruses exist [5]. It has been known for around a century that they exist [6], with the first documented references to viruses occurring in the very late 1800s. Viruses themselves are thought to have existed as long as there has been life on the planet [7, 8].

Viruses are the pathogens responsible for many acute infective episodes. They can affect virtually all organ systems and are frequently noted clinically. Up to 1939, a mere 36 distinct viruses had been noted and separated on immunological grounds, of which 22 could be cultured routinely in laboratories [1]. During the 1940s, a further 26 viruses responsible for human diseases were categorised on serological grounds. Then, in the 1950s, major advances were achieved in instrumentation and other novel techniques, which permitted a further 90 plus viruses to be added to the list of known pathogens. At present, the laboratory detection of viruses has developed to the point where diagnostic tests are highly sensitive and virology is no longer the preserve of academic research [1].

47.4 Epidemiology

In both men and women, irrespective of age, acute respiratory infections are the most prevalent of all diseases. Epidemiological and community-focused research conducted since the early 1900s have ascertained the frequency of these diseases and identified the pathogens responsible. It has been demonstrated that by far the

most common pathogen causing respiratory infections and asthma exacerbations is rhinoviruses. The transmissibility has also been investigated. Recent developments in diagnostic methods have meant that the viral pathogens responsible for respiratory infections can be more precisely identified, with benefits in tailoring antiviral therapy to suit the type of infection [3].

47.5 Aetiology and Pathogenesis

The group of bacteria known to be responsible for upper respiratory tract infections is well-established, and, despite the wide variety of organisms that can infect the sinuses and tonsils, currently all known bacterial pathogens have a degree of sensitivity to existing antimicrobial agents. The same cannot, unfortunately, be said of viruses. Since researchers first became aware of their existence, viruses have been studied intensively. Yet much remains obscure about this class of pathogen, even to the extent of deciding how they evolved and whether they should be classified as living or nonliving. This general ignorance about many aspects of viruses is reflected in the clinical challenges faced when attempting to treat and manage viral infections [9].

47.6 Clinical Characteristics

Whilst there are numerous viruses which can cause infection, the clinical presentation of URTIs tends to be broadly similar for a range of pathogens. More severe symptoms are experienced when viral pneumonia occurs.

47.6.1 Nasal Discharge and Stuffiness

Virtually all upper respiratory viral infections initially present with nasal discharge and stuffiness. Initially the nasal discharge is clear. It may subsequently gain a purulent character with the involvement of bacteria. Nasal stuffiness may accompany nasal hypersecretion as a result of swelling of the conchae. The new coronavirus SARS-CoV-2 can cause a range of effects, the major ones being cough and fever, rather than URT symptoms. However early anosmia has been reported by some patients.

47.6.2 Sneezing

Irritation of the nasal mucosal lining provokes sneezing, a protective reflex that serves to expel pathogens from the nasal cavity. Despite its actually beneficial nature, sneezing is a frequent patient complaint.

47.6.3 Pyrexia

Viral infections can provoke an increase in body temperature that ranges from mild to severe. In the past, it was assumed that a severe elevation in body temperature was indicative of bacterial pathogenic involvement, but it now appears that viruses have evolved which are capable of provoking severe pyrexia, and this sign therefore no longer reliably indicates a bacterial origin to a fever. Pyrexia associated with influenza ranges in temperature from 37.8 °C (100 °F) to a maximum of 40 °C (104 °F). Parents of young children are often extremely alarmed by a marked temperature increase, but children often experience a greater degree of temperature elevation than adults. Pyrexia is also associated with a subjective sensation of feverishness, which may comprise chills, sweating or the sensation of being cold in spite of actual body temperature rises. Pyrexial duration is typically less than 7 days, with the majority of episodes persisting for 3 or 4 days.

47.6.4 Cough

A dry, persistent cough may accompany upper respiratory infections. Some upper respiratory virus infections also involve the lungs. The cough may worsen, becoming uncomfortable and painful. Patients may also experience shortness of breath or chest discomfort during this time. The usual duration of an influenza-related cough is approximately 2 weeks.

47.6.5 Headache

A severe headache may herald the onset of a viral URTI. On occasion, ocular or auditory symptoms, such as photophobia or phonophobia, may accompany the headache.

47.6.6 Muscular Ache

Muscular ache is a frequent occurrence, particularly the neck, back and limbs. The pain is frequently of sufficient severity to render movement distressing, even routine basic activities. Lethargy and apathy are extremely frequent symptoms in URTI but are also common in other conditions, too. Malaise is common to multiple conditions, including URTI. These symptoms may have a very rapid onset and can prove challenging to manage.

47.6.7 Diarrhoea and Vomiting

Although it is not especially characteristic of respiratory viral infections, diarrhoea and vomiting have also been reported amongst non-respiratory symptoms of coronavirus (COVID-19) infections in China.

47.6.8 Hyposmia and Anosmia

Loss of the sense of smell can follow a viral cold and is sometimes permanent. Anosmia has been reported as an early symptom of COVID-19, with inflammation confined to the olfactory area seen in a CT scan from one Chinese patient. This needs confirmation.

47.7 Diagnosis

The majority of patients suffering from a URTI are aware of the cause and do not seek medical care other than visiting a pharmacy. They are generally looking for symptomatic relief, rather than a diagnosis. If a physician is consulted, the majority of URTIs can be identified from an appropriate patient account and by routine oto-rhinolaryngological physical examination. The pharynx may be swabbed to identify a bacterial pathogen. Group A β-haemolytic streptococci may be identified using rapid antigen detection techniques. If URTI increases in severity, it may presage pneumonia or bronchitis, in which case radiological confirmation by plain x-ray or CT may be required.

47.7.1 Detection of Virus

Accurate diagnosis of infections of coronavirus disease 2019 (COVID-19), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) is of paramount importance in mapping outbreaks and for efficient measures to prevent further spread. Given the current lack of efficacious pharmacotherapy for coronavirus infection, diagnostic confirmatory tests are of limited use in clinical management, other than randomised trials of therapy.

Techniques which can swiftly and accurately detect all of the recognised strains of coronavirus in humans have only recently become available. Such methods include reverse-transcriptase polymerase chain reaction (RT-PCR) and immunofluorescence antigen detection assays [10, 11].

Since the polymerase technique is capable of identifying each of the four coronavirus variants found in humans, it has now mainly replaced other ways of detecting the presence of the virus. There are PCR primers available suitable for all types of coronavirus, but they lack the specificity of primers tailored for each individual quasi-species [11–13]. The method is more sensitive when used in a real-time fashion [14]. Tissue culture is challenging for viruses of the wild type found in the community.

47.8 Treatment

The management of severe viral RTIs is currently focused on preservation of respiration and alleviation of life-threatening conditions such as renal failure, myocarditis and disseminated intravascular coagulation.

For URTIs nasal decongestants make it easier to breathe. Headaches are treated with pain killers. Paracetamol and the NSAIDs are effective in reducing pyrexia and myalgia. It is recommended to inhale steam and gargle with salt water. Antitussives and expectorants may be required in particular cases.

For certain serious URTIs, antiviral medication is indicated as these agents can mitigate the symptoms and lessen the duration of illness. However, there are numerous causative pathogens involved, few of which are affected by currently available antiviral drugs. The search for effective therapy demands rapidly organised controlled trials.

47.9 Prevention

47.9.1 What Can Be Done to Prevent Acute Upper Respiratory Infections?

Regular use of intranasal saline reduced the frequency of URTIs in an open study by Tano and Tano [15]. Sixty-nine recruits found daily physiological saline significantly ($p = 0.027$) reduced the number of days with nasal secretion and/or blocked nose (mean 6.4 days) compared to the observation period (mean 11 days). Furthermore, the participants had a mean of 0.7 episodes of upper respiratory tract infection during the spray period, compared with 1.0 episodes during the observation period ($p = 0.05$).

Professor Ron Eccles, former director of the Common Cold Centre in Cardiff, advocates keeping the nose warm with a protective scarf in cold weather to prevent nasal drying which reduces mucociliary clearance. There is a nasal spray (Vicks First Defence) that claims to prevent colds, reducing the chance of a full-blown cold by up to 50% if taken at the first sign of symptoms and cutting symptom severity by 40%. The treatment, which is not a drug, works by trapping the virus in a viscous gel, disarming it and allowing eradication by mucociliary clearance.

For COVID-19 washing hands regularly with soap and water has the greatest protective effect as it removes the lipids in the outer wall of the coronavirus [16–18]. Some other ways to reduce transmission are:

- Avoidance of contact with sick individuals [19]. Persons caring for them need adequate protective equipment.
- Social distancing, since asymptomatic individuals can transmit the infection.
- Use of wipes on objects that may be touched by more than one person, including the infected individual. Such objects may include remote control devices, telephones and door handles. Wearing disposable gloves can help.
- The affected individual should cover his or her mouth and nose.

47.9.2 Recent Measures to Prevent 2019-nCoV (See Also Sect. 47.9.3)

Recently, the strategy to contain COVID-19 has involved case detection and identifying the contact network, as well as screening individuals travelling between different countries, particularly those coming from areas where outbreaks have occurred. Whilst these actions have proven insufficient to stop COVID-19 becoming a pandemic, the aims are to:

1. Lessen the rate at which transmission occurs.
2. Allow a longer period for people in general, and healthcare personnel in particular, to be prepared for the disease burden from the disease affecting very large numbers of people.
3. Allow a fuller appreciation of the nature of 2019-nCoV on which to base public health strategy and clinical response, namely, detection methods, possible drug treatments and vaccination [17].

47.9.3 Coronavirus 2019

Coronaviruses (CoV) consist of numerous viruses capable of producing a variety of diseases, from coryza to conditions of greater severity such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV). A novel coronavirus (nCoV) refers to a previously unknown virus type capable of infecting human beings. Coronavirus infections are zoonoses, in other words, diseases which pass from an animal to a human. Intensive research has uncovered the transmission from civet cats of SARS-CoV and of MERS-CoV from dromedary camels. There exist a number of coronavirus strains which currently infect animals but have not yet been transmitted to human beings [18].

47.10 What May Happen in the Near Future During an Outbreak?

During an outbreak, cases generally increase on a daily basis. If it is possible, human-to-human transmission becomes the dominant mode of viral transmission. This places a high burden on medical facilities, which experience a surge in demand. Schools, daycare facilities, workplaces and other settings in which people collect together may be less crowded than usual or may need to be closed for some time, together with other places such as nonessential shops, restaurants, theatres, cinemas, churches and mosques, i.e. anywhere people congregate. The public healthcare infrastructure may be overstretched, if admissions to hospital and fatalities increase beyond a certain level. This may also produce a detrimental effect on other public services, e.g. the police, accident and emergency and public transport systems. Collapse of such services is a potential risk, as is collapse of the economy. In the case of COVID-19, the lack of suitable

pharmacotherapy and a vaccine mean that management needs to rely on nondrug interventions [19].

47.11 What Is the Longer-Term Outlook for Emerging Viral Infections?

Disturbances within ecosystems that have led to the emergence of novel human pathogens within the last decades seem set to persist for the foreseeable future. Such disturbances include deforestation to increase available agricultural land, more intensive cattle farming, globalisation, the sale of bush meat and the continued growth of cities. On that basis, it seems probable that novel pathogens will keep emerging as these trends continue [20].

A review of every novel pathogen identified from 1980 onwards reveals patterns in the type of pathogen involved. There are four features anticipated to be present in most newly emergent infections:

- Viral pathogens are likely to be RNA-based, as the majority have been so far.
- The majority are zoonoses, with animal (especially mammalian) reservoirs.
- Viruses will usually already infect a variety of different animal hosts before becoming transmissible to humans.
- The virus should be at least partially capable of human-to-human transmission, even if initially this transmission is not very efficient. As the virus evolves and the pattern of human exposure changes, a limited number of cases may become an epidemic [20, 21].

These four characteristics are broad general trends, but there are historical examples that appear to buck the trend, such as the apparently sudden emergence of syphilis in Europe in the late 1400s. It is still not certain where the pathogen originated, but it is known to be a bacterium without an animal reservoir of infection. Despite such counterexamples, the four characteristics still have use as a general indicator of the type of novel pathogen to expect in the future [20, 21].

47.12 Surveillance

Swiftly detecting cases and identifying the pathogen is the vital first step in containing emergent infections. The experience gained in the BSE (bovine spongiform encephalopathy) and SARS crises has provided valuable real-world insights into how swift detection and case confirmation can be used to put prophylactic measures in place in a timely fashion [22, 23]. Virtual modelling of potential pandemic influenza appears to show that unless detection is very rapid and prophylactic measures are adopted without delay, stopping the spread of an epidemic becomes less and less likely [24].

Nonetheless, obtaining a clear overview of emergent infections is not without difficulty. In the first instance, surveillance will probably rely on reported observations made by clinicians, e.g. a case series with atypical features in common. It is also feasible to use the Internet to collate reports of novel pathological features. In the more distant future, diagnostic equipment capable of detecting all recognised human viral pathogens should be in use. An example is the so-called lab-on-a-chip [25].

As it is clearly indicated, emergent pathogens arise right across the globe, and spread in an age of ever-increasing international travel and cross-border trade is likely to be global. This was the case with the SARS epidemic. The emergence of viral pathogens is a global problem calling for a global response.

47.13 Multidisciplinary Aspects

Looking at the catalogue of emergent viral infections so far, we can perceive the fundamental significance of animal reservoirs. A corollary of this is that monitoring of the reservoir of infection in animals helps guide risk management in human beings [26]. A novel pathogenic agent in humans is likely to be better known initially to veterinary science [27]. Some examples of this zoonotic basis include neoplasia linked to infection, retroviral and lentiviral infections, transmissible spongiform encephalopathies, rotaviruses and papillomaviruses, with the potential addition of coronaviruses and ehrlichiosis. It is becoming increasingly accepted that pathogens in humans are mostly identical with those found in other animal species [28].

Schwabe argued in 1969 that veterinary and human medicine should be seen as "one medicine", a theory that resonates powerfully with virology researchers who have an interest in emerging pathogens.

Whilst the biological science underlying the host-pathogen interaction in humans and emerging pathogens is undoubtedly central to an appreciation of the phenomenon of disease emergence, the concept of ecological disturbance plays an equally important part. Ecological refers to a wide variety of elements that can drive disease emergence, in particular, environmental alteration, changes in agriculture, arthropod vectors (including insects), human population changes, specific behaviours, culture, the economy and sociological factors. To give some specific examples, one might note the role of bush meat trading in fostering HIV and SARS, agricultural feeding practices in BSE and vCJD (variant Creutzfeldt-Jakob disease) and different methods in pig raising, which inadvertently promoted Nipah virus. What these examples reveal is that many academic disciplines can contribute to knowledge of novel pathogens and explanations need to be multilayered. Researchers will need to build working relationships with colleagues both veterinary and medical, as well as in a broad spread of academic departments.

47.14 Conclusions

Understanding previous outbreaks is the only way we can predict what may happen in the future. Studying the four levels which comprise the pathogen pyramid helps to guide thinking about how epidemics by new pathogens can occur. It needs to be admitted, however, that the individual levels are themselves often incompletely understood.

The bottom layer of the pyramid concerns exposure, an area in which current knowledge is particularly deficient. The full range of potential pathogens is largely unknown, but systematically evaluating each environment where exposure can occur, particularly to mammalian zoonoses, is one way forward. Shotgun sequencing may be of value here.

Then there is the problem of working out in advance which pathogens possess the ability to cross the species barrier. At present, receptors by which they can enter human cells have been identified in only 50% of the 189 known human viral pathogens. Discovering the receptor for all cases will assist the predictive process.

The pyramid's third level relates to transmissibility between humans, and the efficacy of this process is only knowable by detailed evaluation of the earliest outbreaks. These evaluations may provide vital clues as to the population most at risk. Analysing the figures on affected individuals as they become available gives an indication of how transmissible the pathogen has become. Such data are frequently lacking for pathogens which rarely infect humans, and it may be unknown whether human-to-human transmission occurs. Viral mutation may also alter the transmission potential.

The probability of novel pathogens emerging in the near future is close to 1. The scientific and logistical resources need to be in place to manage such outbreaks as and when they occur.

The experience of SARS, H1N1 influenza and Ebola to date gives some grounds for a cautious optimism about our ability to contain outbreaks. However, much remains to be done to ensure the current COVID-19 pandemic does not kill as many as the Spanish influenza one of a century earlier. Surely we have learnt enough in the interim to improve our performance?

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Computational Fluid Dynamics: Analysis of a Real Nasal Airway

48

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48.1 Introduction

The development and use of personalized medicine have an increasing importance in patient care. Numerical simulations of various biological phenomena have and continue to enable doctors and medical specialists to diagnose patients and understand how practical and effective treatment can be. The paths to patient-specific diagnosis and preoperative planning are slowly being paved and with immense success. Proof of this lies in the major developments made in medical software that have enabled accurate three-dimensional (3D) models of the human organs to be generated for use in analysis, ensuring accurate results. Also, advancements in technology have enabled simulation of surgeries where professionals can make cuts, test out different implant sizes and do much more to the models of organs. This helps the medical practitioner find out the effects of the procedure beforehand by performing analysis of the modified model.

Breathing is a dynamic process between inhaled air, mucosal surfaces and the alveoli. Within the nasal cavity, there are changes of airflow and pressure occurring during the respiratory cycle, as well as exchanges of heat and humidity, and important immune responses to inhaled antigens and allergens [1]. However, evaluation of nasal function with anterior rhinoscopy, nasal endoscopy and/or paranasal CT scan is usually insufficient to make proper assessment of airflow, air-surface interaction and olfaction. There are currently two clinical measurement tools to evaluate airflow parameters: Rhinomanometry measures pressure and airflow during respiration to define the resistance of the nasal airway. Acoustic rhinometry uses the sound

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_48

waves reflected from the nasal walls to create a two-dimensional image of the nasal cavity. These tests have significant limitations since they do not show the entire nasal function, such as local flow and pressure changes, turbulence and heat exchanges [1, 2]. As nasal cavity has a complex geometry which hinders placement of pressure, temperature and humidity sensors throughout the flow, we need a non-invasive and objective method to measure or calculate those parameters.

The utilization of computational fluid dynamics (CFD) for airflow studies has opened a new era. The noninvasive nature of CFD modelling permits us to explore a broad variety of flow simulations, consequently allowing us to monitor pressure and stress variables. More recently, numerical simulations have been increasingly applied to study flow patterns in airways with anatomic abnormalities. By using CFD modelling, quantitative and qualitative information can be obtained on various parameters of airflow, such as flow velocity, static airway wall pressure and pressure drop, turbulence and wall shear stress [3, 4]. The first anatomically accurate 3D computer-generated model of airflow in the nose based on CT scan results was described in 1995 [5]. Since this time CFD modelling has been used to study airflow, heat and humidity exchanges, as well as topical delivery of drugs into the nasal cavity and paranasal sinuses under normal or pathological conditions [1].

In this chapter, the focus is placed on personalized nasal surgery and how the procedure has been enhanced with numerical simulations of respiration. We will venture into details of normal physiologic respiration through the nose and how numerical simulations help as a predictive tool.

48.2 Methodology

48.2.1 Construction of Airway Model

A three-dimensional (3D) anatomically precise patient-specific model is reconstructed from multidetector-computed tomography (MDCT) images of an anonymous maxillofacial scan, from the PACS archive. Volumetric DICOM images with 0.1 mm intervals were carried to commercial medical imaging software, MIMICS® (Materialise, Belgium). The model generated includes the nasal cavity, paranasal sinuses and the nasopharynx. The process begins as CT scans of the subject are loaded into MIMICS and the nasal cavity and airway are identified in each of the axial images based on a predefined thresholding relative to the surrounding tissue. 3D raw models are reconstructed from these masks by surface triangulation and then exported into 3-matic, another Materialise software module. Different views of 3D model obtained are shown in Fig. 48.1.

In 3-matic, the model's boundary conditions are defined and demarcated as individual faces. An inlet, outlet and wall from the 3D surface model are specified by creating a datum plane. Separate datum planes are used for each surface, so that separate boundary surfaces are defined. The datum planes are then appropriately positioned against the 3D model to mark where the boundary surfaces will be created. By using the cut function, under the 'Design' tab, the model nasal cavity is

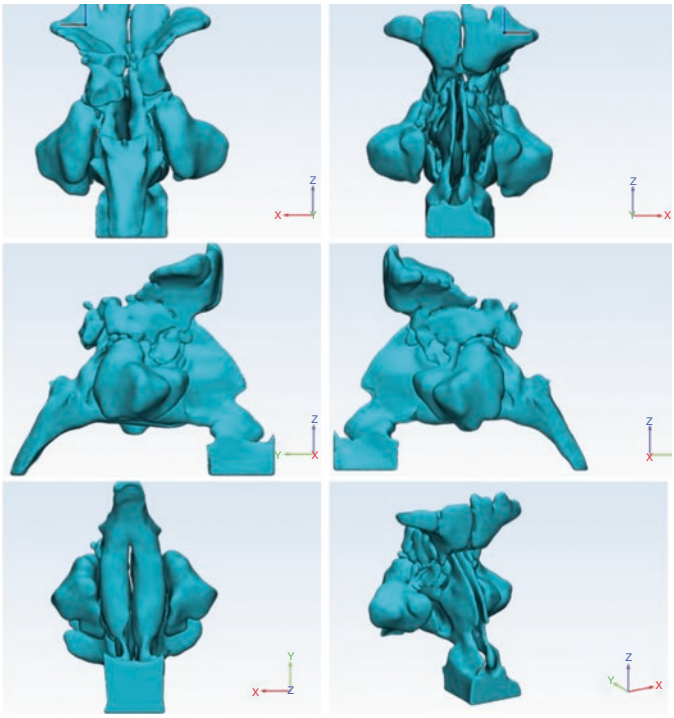

Fig. 48.1 3D model of the nasal cavity, paranasal sinuses and nasopharynx (different views)

then cut into separate parts. The parts that are not needed are then deleted and new surfaces created as a result (Fig. 48.2).

Using the 3-matic software, the surface mesh quality can be improved by smoothing and remeshing, to control the maximum cell edge length and the grid density. Remeshing should be performed after the boundary surfaces are defined, to avoid any changes in the new mesh. The surface mesh should be generated first. The 'Remesh' tab has a variety of options for the type of surface mesh that can be developed. Depending on the grid size and the complexity of the model, a specific type or a combination of mesh types should be chosen. In the current study, an adaptive mesh was generated. The volume mesh was then created.

48.2.2 CFD Modelling

The generated mesh is imported into ANSYS Fluent® (Canonsburg, PA, USA) for analysis to be performed. ANSYS Fluent implements the finite-volume method to solve conservation equations. The pressure-velocity coupling is done by means of the SIMPLE-type fully implicit algorithm. Pressure-velocity coupling is used with a predictor-corrector pressure scheme. The solution is second-order accurate in

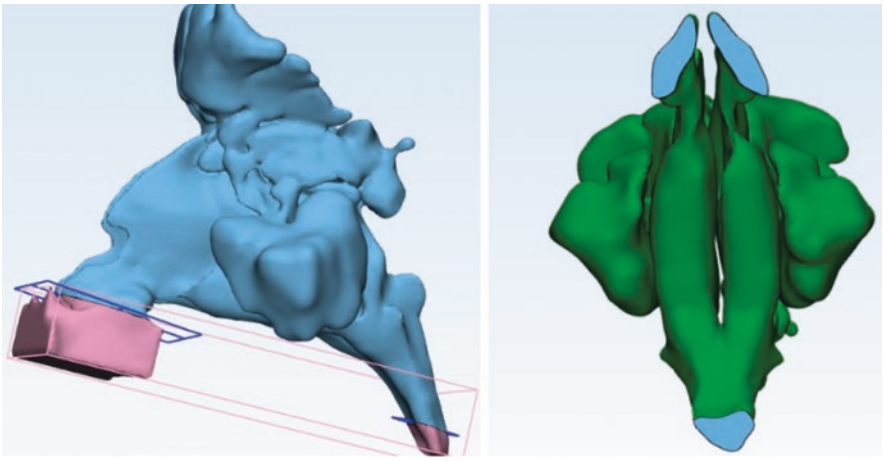

Fig. 48.2 Defining boundary surfaces in 3-matic® (Materialise, Belgium) software

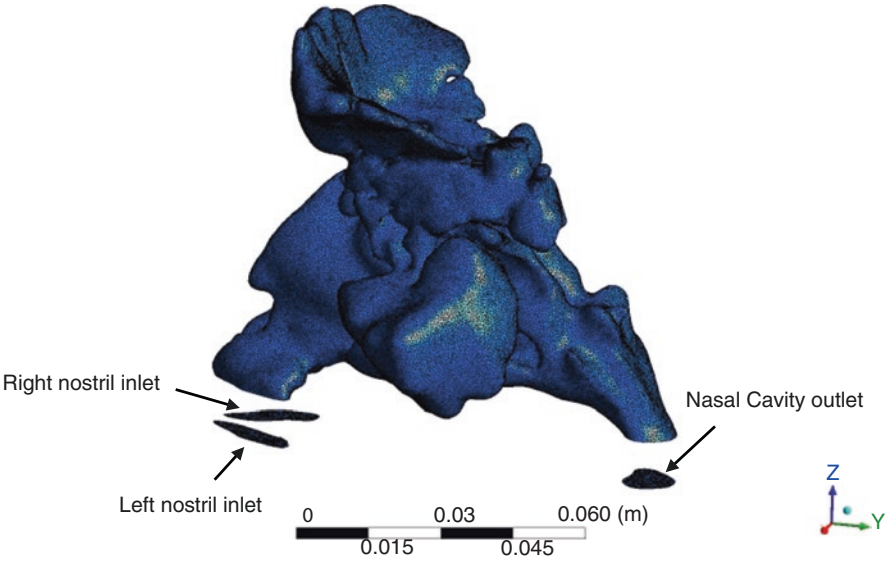

Fig. 48.3 Mesh generated in 3-matic® (Materialise, Belgium) software

space. For the current case study, 3D steady Navier-Stokes equation with the $k - \omega$ turbulence model is used to solve the airway. The mesh comprised of 483,663 cells, 1,072,202 faces and 132,773 nodes (Fig. 48.3).

For boundary conditions, the nose inlets are defined as pressure inlets and assigned 0 Pa as gauge pressure (standard atmospheric pressure). No slip boundary conditions are defined for the inner wall, while the nasal cavity outlet/nasopharynx

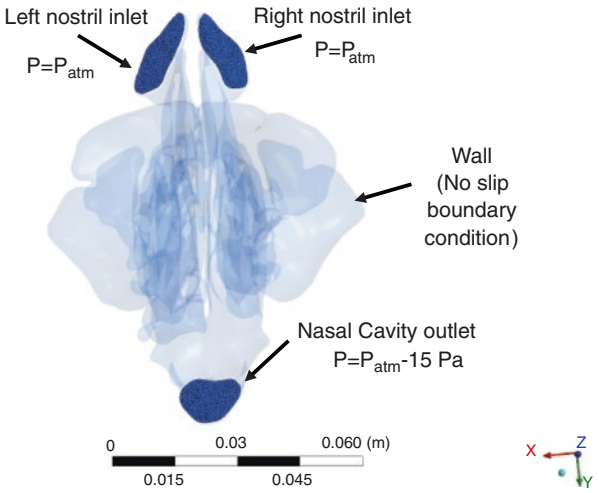

Fig. 48.4 Boundary conditions

is set as a pressure outlet and assigned with −15 Pa as gauge pressure. Figure 48.4 shows the boundary conditions at the nose inlets (nostrils) and the nasal cavity outlet. Atmospheric pressure is taken to be P_{atm} = 101,325 Pa.

48.3 Results

48.3.1 Geometric Representation for Post-processing

The geometry of the nasal airway is very complex. For this purpose, the post processing is performed at specified planes in different plane sections. The model is investigated along the CORONAL, AXIAL and SAGITTAL planes. All the investigated plane sections are shown in Fig. 48.5, while the 2D plane sections corresponding to CORONAL, AXIAL and SAGITTAL planes are shown in Fig. 48.6a–c, respectively. The areas of the various plane sections are tabulated, and the values are shown in Table 48.1. As for the boundary surfaces, the areas are shown in Table 48.2. Note that the right and the left nose inlets have slightly different areas (see also Fig. 48.4). This is important to note because this will be elicited by the resulting velocity and pressure contours drawn at the nostril planes.

48.3.2 Streamlines

Streamlines are drawn to illustrate the flow of air within the nasal cavity (Fig. 48.7). The three-dimensional streamlines indicate that the main flow path is through the inferior meatus. Around the nasal valve and the nasopharynx, the flow is faster than

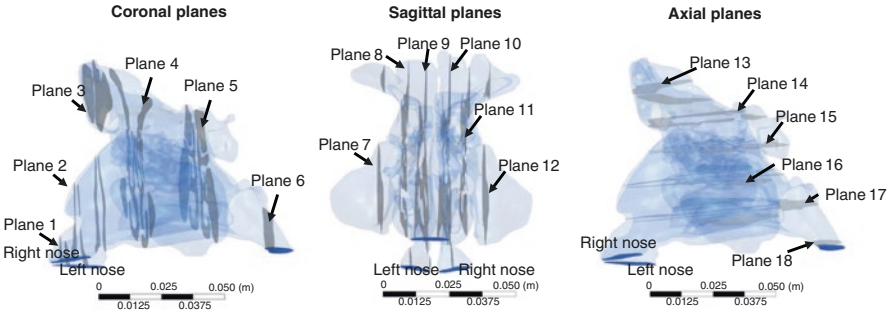

Fig. 48.5 3D model investigated at different plane cuts

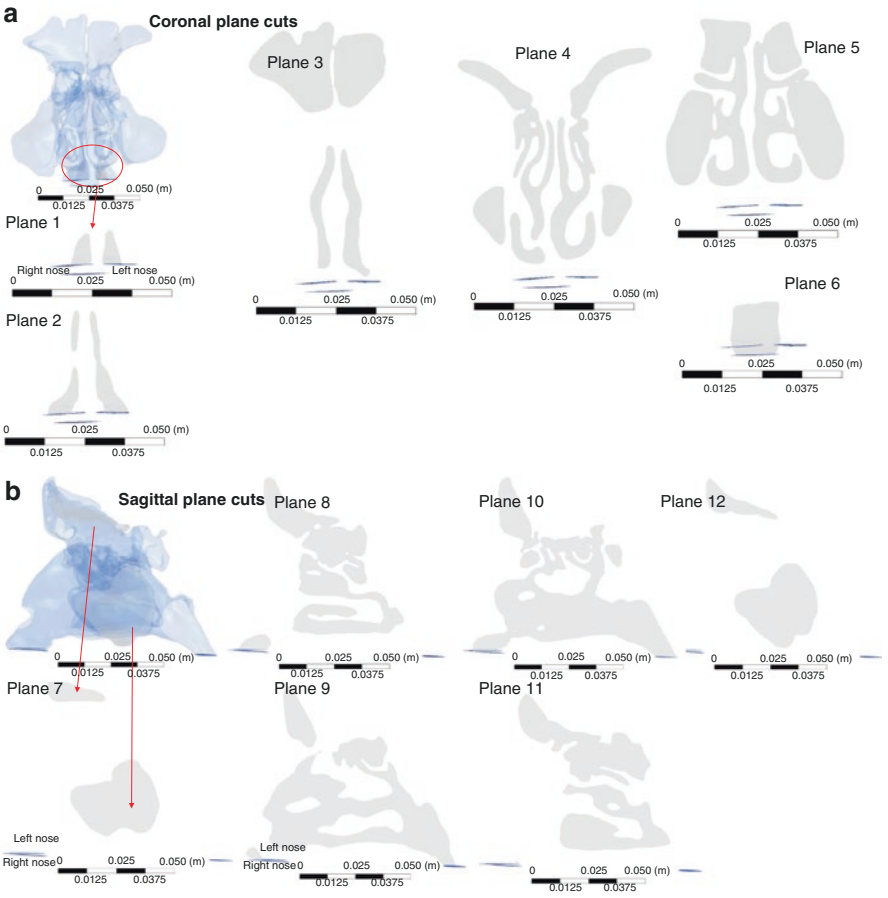

Fig. 48.6 (**a**) Coronal plane cuts. (**b**) Sagittal plane cuts. (**c**) Axial plane cuts

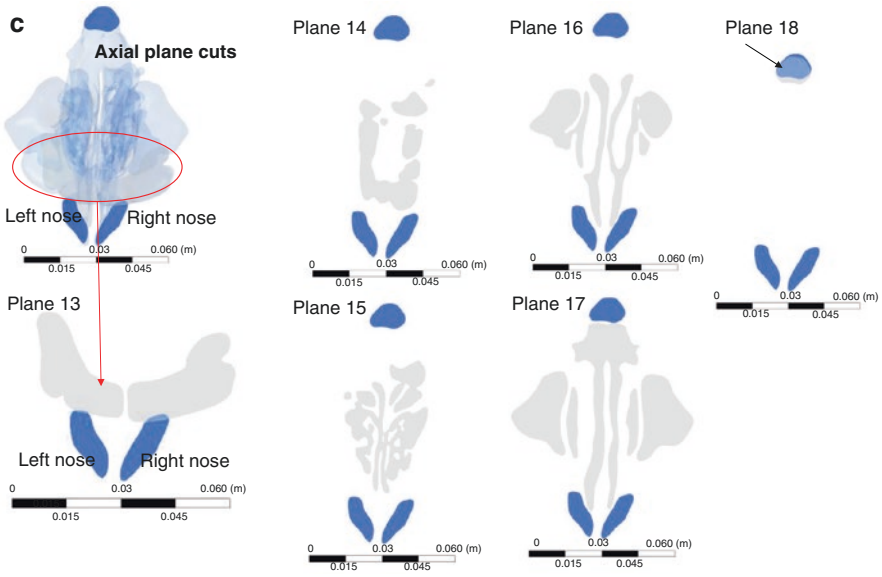

Fig. 48.6 (continued)

Table 48.1 Various plane section areas

Planes	Area (m^2)					
Planes 1–6	0.000088	0.000203	0.00106	0.00117	0.00165	0.000232
Planes 7–12	0.000996	0.00171	0.00239	0.00262	0.00169	0.00110
Planes 13–18	0.000778	0.000682	0.000855	0.00114	0.00198	0.00013

Table 48.2 Boundary surfaces areas

Boundary surface	Right nose inlet	Left nose inlet	Nasal cavity outlet
Area (m^2)	0.0001093	0.0001113	0.0001162

the turbinate section area. The region with the highest velocity is spotted near the choana, the nasopharynx region, where the streamlines elicit this behaviour. There are also sections where vortices are experienced, on the top and bottom sections of the nasal valve and middle turbinate. The formation of the vortices creates at the same time very low suction pressure regions and also increase in the wall shear stresses.

Left and right frontal vortices are generated just after the left and right noses, respectively (Fig. 48.7a, b). The flow initially accelerates in front of these vortices, and then two dominant vortex structures with low pressure cores are visualized in front region of the airway. The streamlines also show a high velocity region before the nasal cavity outlet (Fig. 48.7a). Figure 48.7b also represents the vortex structures formed at both maxillary and frontal sinuses.

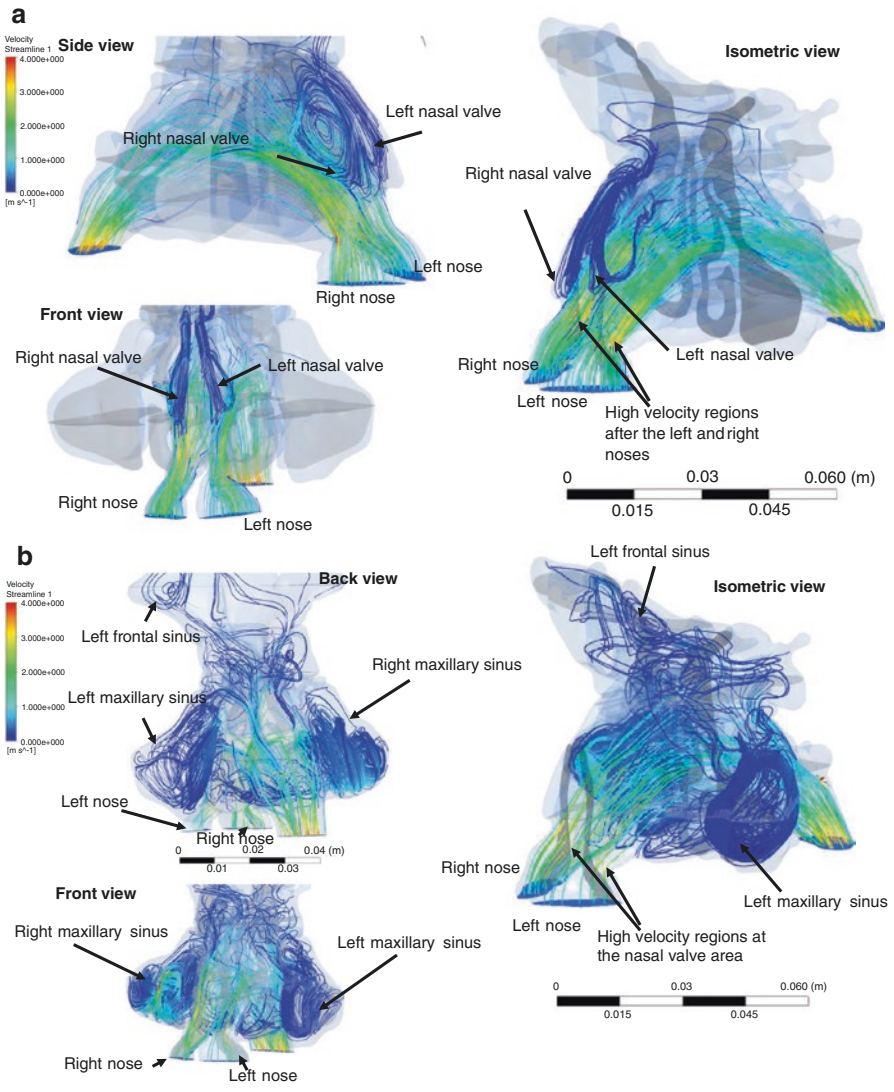

Fig. 48.7 (**a**) Streamlines showing the front vortices. (**b**) Streamlines showing the paranasal sinus ventilation during inspiration

48.3.3 Velocity and Pressure Contours

Velocity magnitude contours for the CORONAL plane cuts are plotted in Fig. 48.8. The contours are drawn at their local contour values to be able to visualize high velocity regions and local pressure drops at each section. The range for the pressure stays within the limits defined as boundary conditions. As expected, the gauge

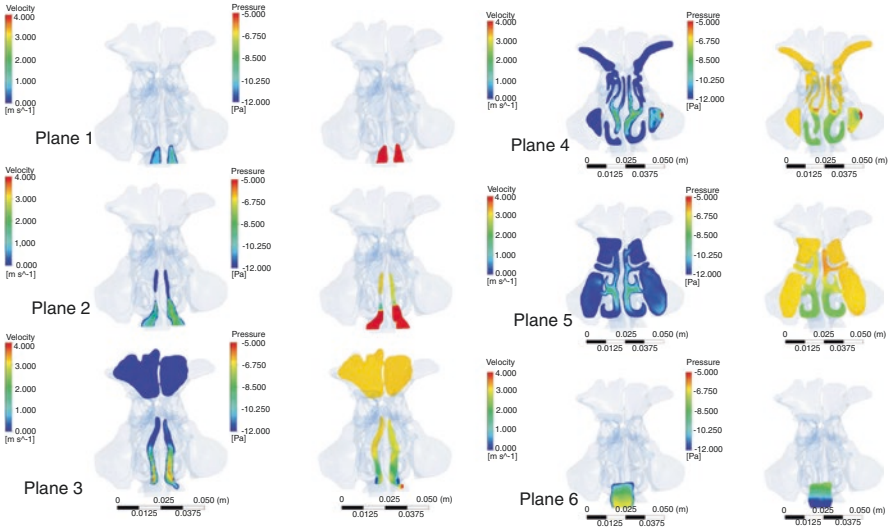

Fig. 48.8 Velocity magnitude (left) and gauge pressure contours (right) in coronal planes

Table 48.3 Average and maximum velocities at the planes

Planes	Average velocities (m/s)					
Planes 1–6	0.971	1.28	0.602	0.346	0.336	1.93
Planes 7–12	2.58×10^{-2}	0.338	0.942	0.790	0.266	0.0608
Planes 13–18	0.00678	0.0772	0.165	0.587	0.609	2.85
Planes	Maximum velocities (m/s)					
Planes 1–6	1.83	7.13	4.68	9.41	2.83	3.42
Planes 7–12	0.382	4.23	3.70	**12.8**	2.03	0.537
Planes 13–18	0.0530	0.470	1.37	5.84	3.55	3.60

pressure gradually decreases from 0 (atmospheric pressure) to −15 Pa as the sections get closer to the nasal cavity outlet.

The average and maximum velocities of each plane along CORONAL, SAGITTAL and AXIAL are also shown in Table 48.3. Along the CORONAL plane, through planes 1 to 6, the average velocity is observed to increase gradually from 0.971 m/s to 1.28 m/s and then decrease while until a high velocity of 1.93 m/s is reached close to the nasal cavity outlet. Along this cut a maximum velocity is observed at plane 4 with 9.41 m/s.

When observing the cuts along SAGITTAL plane, it is observed that the velocities reach maximum value of 12.8 m/s on plane 10 (see Figs. 48.9, 48.10 and 48.11).

Average pressure values on the planes were computed and tabulated in Table 48.4. The pressure values obtained reflect the data stated earlier. The sections closest to the nasopharynx show the lowest values of pressure achieved, for instance, plane 6

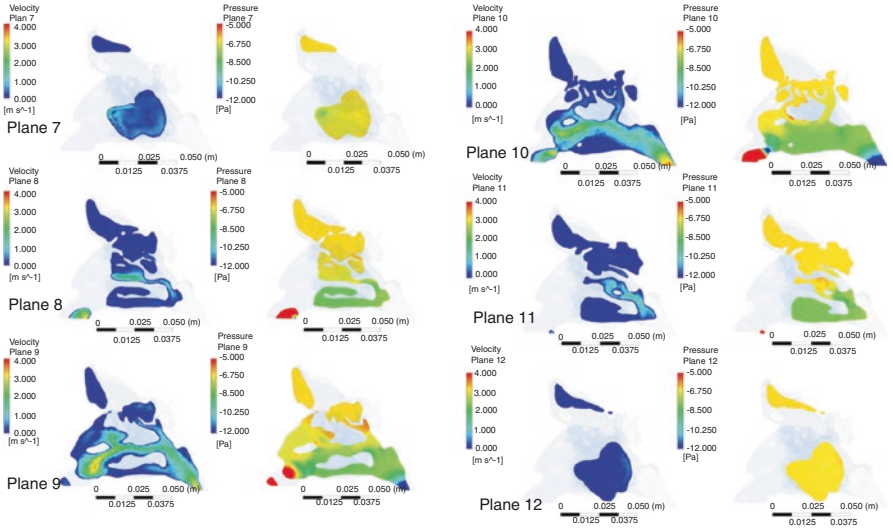

Fig. 48.9 Velocity magnitude (left) and gauge pressure (right) contours in sagittal planes

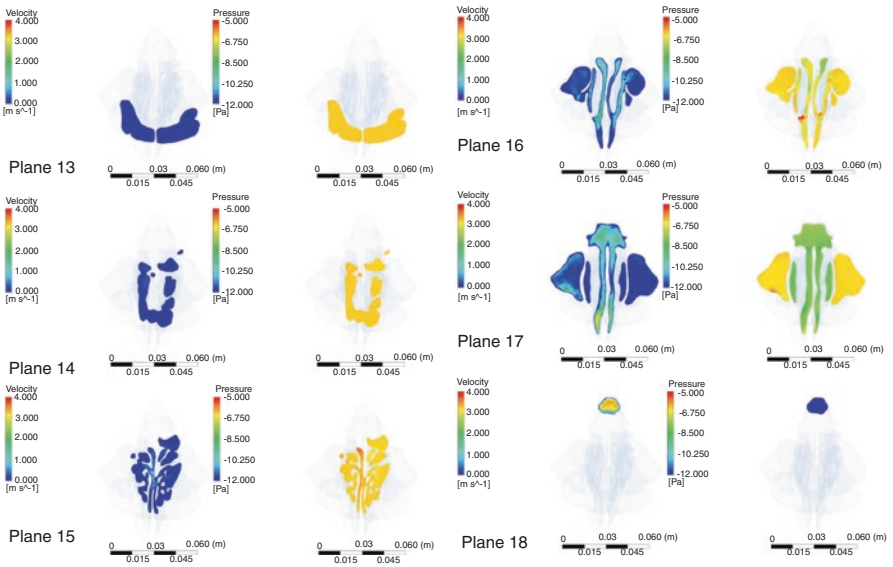

Fig. 48.10 Velocity magnitude (left) and gauge pressure (right) contours in axial planes

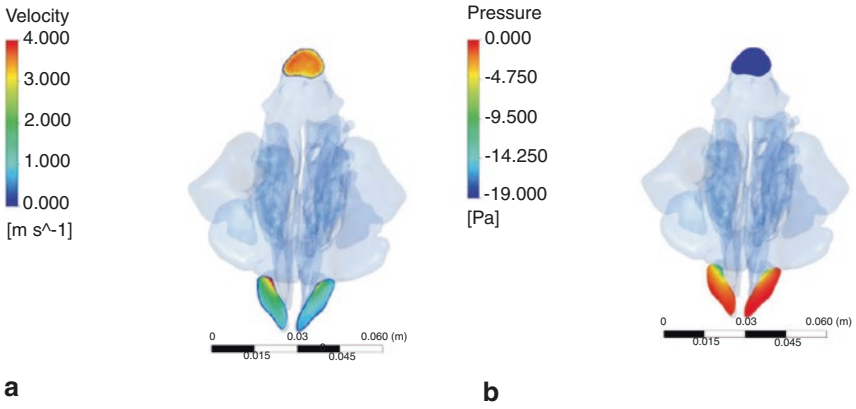

Fig. 48.11 Velocity magnitudes (**a**) and gauge pressure (**b**) contours for boundaries

Table 48.4 Average gauge pressure values at the planes

Planes	Average gauge pressure (Pa)					
Planes 1–6	−0.993	−4.61	−6.69	−6.71	−6.72	−10.4
Planes 7–12	−6.31	−6.79	−6.97	−7.11	−6.98	−6.38
Planes 13–18	−6.32	−6.33	−6.31	−6.56	−7.37	−13.4

Table 48.5 Average velocity values at the boundaries

Boundary surface	Right nostril	Left nostril	Nasal cavity outlet
Velocity (m/s)	1.755	1.183	3.388

Table 48.6 Average gauge pressure values at the boundaries

Boundary surface	Right nostril	Left nostril	Nasal cavity outlet
Pressure (Pa)	−1.067	−2.263	−15.0

registers a value of −8.212 Pa which is the lowest average, closest to −15 Pa. In contrast, plane 1 registers the highest value of pressure with −1.082 Pa as the value. This is in accordance with expectations. The average values of the velocity at the nose inlets and nasal cavity outlet are computed and shown in Table 48.5. The average values of the pressure on all the boundary surfaces are computed and shown in Table 48.6.

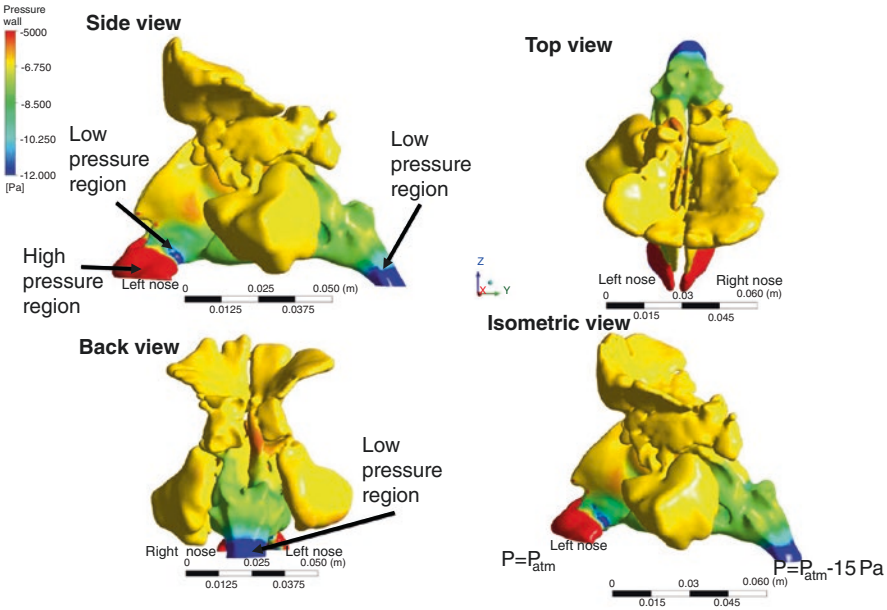

Fig. 48.12 Gauge pressure distribution of the wall

48.3.4 Wall Pressure and Shear Stress Values

For the wall, only shear and pressure contour are plotted. The gauge pressure on the nasal wall is shown in Fig. 48.12. The pressure at the nose inlets is close to atmospheric pressure, and positive pressure values are also observed in the nose regions. The outlet section has −15 Pa gauge pressure as it is given in the boundary conditions. A low-pressure region is also observed just after the nose region.

For wall shear stress is plotted in Fig. 48.13, and the highest wall shear stresses are observed just after the nose inlets and also at the outlet region where the pressure is lowest.

48.4 Discussion and Literature Review

The nose is a dynamic filter that provides humidification, thermoregulation and filtration of the inhaled air, as well as the olfaction function and important immune responses to inhaled antigens. Therefore, complex anatomy with vascular and neural supply of the nose is crucial for executing such a complex function, and of course, there are several things that can go wrong in this complex and delicately balanced system.

Evaluation of nasal patency requires thorough examination with anterior rhinoscopy, nasal endoscopy and paranasal sinus CT that is usually asked to evaluate

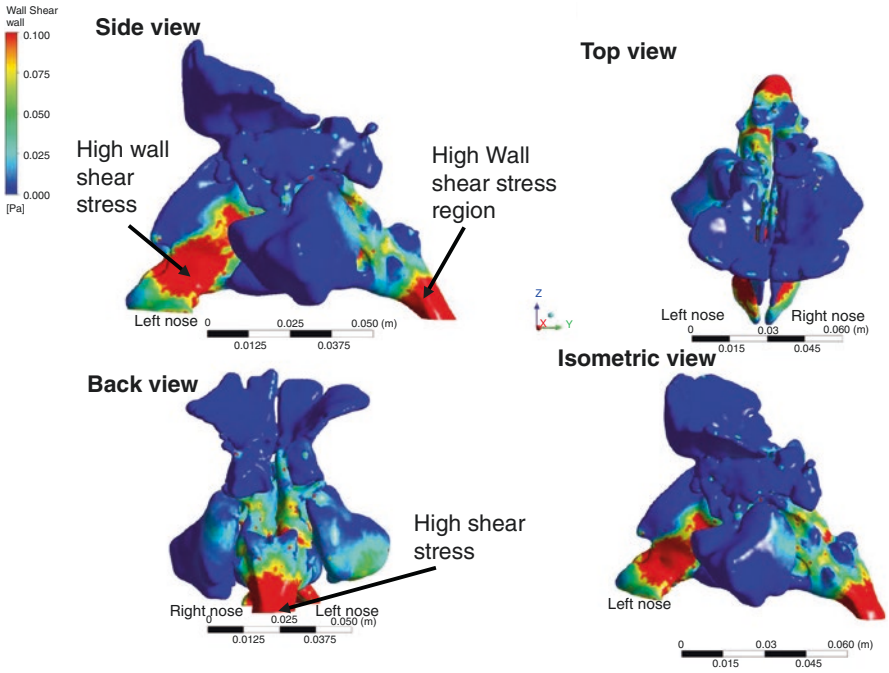

Fig. 48.13 Wall shear stress on the wall

paranasal sinus ostia. Acoustic rhinometry and rhinomanometry can measure cross-sectional areas in nasal cavity and define changes in overall nasal resistance and flow. However, these studies are not able to show sufficient details of dynamic airflow due to the structural complexity of human nose and nasal pathologies. These details can partly be determined by CFD, which enables modelling airflow and air-mucosa interaction by numerical solution of fluid dynamics equations.

Accurate 3D models of the nasal cavity and upper airway have already been seen in literature. For a study performed to investigate how airway geometry affects internal pressure in the upper airway of patients with obstructive sleep apnoea syndrome, an accurate model of the airway is investigated with the region of concern, from the nasopharynx to the hypopharynx by Xu et al. [6]. In another study, to validate the use of computational fluid dynamics (CFD) for human upper airway flow simulations, a precise model of the nasal cavity and the upper airway is provided and used for analysis [7]. Analysis was performed on a 3D sinonasal model of a healthy adult and CFD simulations performed to assess pressure, velocity, wall shear stress and particle resident time. The obtained values helped in better understanding the biological phenomena surrounding the sinuses during respiration [8].

To investigate nasal physiological processes like inspiration, expiration and sniffing, a study was performed on an anatomically exact 3D model of the nasal

and pharyngeal cavity of a healthy adult. Unsteady Navier-Stokes equations were solved and velocity and streamline distribution of airflow visualized. The results distinguished the differences between the types of flow and the olfactory areas they pass through [9]. In another study, airflow dynamics during coughing are investigated. Computer tomography (CT) scans of a patient coughing are obtained and a 3D model of the upper airway and main bronchi generated. From the results, it is determined that there is a linear relation between the maximum velocity, pressure and wall shear stress with the cough peak flow rate [10]. Even the deposition of particles has been evaluated, an important aspect in inhaler drug therapy used to determine where particles that are inhaled will be deposited/settle. The particle deposition for light, normal and heavy breathing is investigated and presented [11]. These and more studies have all been simulated to mimic reality, depict various processes and procedures and help predict what should be done.

Various works focused on personalized nasal surgery and virtual surgery and how CFD simulations aid in preoperative planning have been published. Some works also investigate how efficient a procedure is by performing analysis on CT scans obtained from patients who had undergone the procedure. For one case numerical simulation was performed on the middle turbinate section of the nasal vault of both preoperative and postoperative 3D models generated from CT scans of a patient to investigate the effect on nasal airflow dynamics if a resection is performed. Analysis was carried out for quasi-steady laminar nasal airflow at resting breathing conditions. Focusing on velocity, streamlines, shear stress and pressure drop, it was concluded that for the patient in question, the middle turbinate resection did not affect the overall nasal airflow. Therefore, it was pointed out that CFD analysis can be used as a planning tool to guide the optimization of airflow [12]. It is highlighted that CFD would provide a safe, cost-effective and patient-centred tool in virtual surgery and preoperative planning [13].

Therefore, simulations provide a doorway to reliable patient-specific diagnosis and treatment. Note that studies have been performed to validate the use of CFD to simulate upper airway flows. Also, in an earlier mentioned study, to validate the use of CFD in human upper airway flow simulations, the results obtained from analysis are compared to those obtained from experiments done on a model built from stereolithography. Pressure and velocity values are measured, and the simulation and experiment are carried out with the same conditions. Several numerical approaches are used in CFD during analysis and the authors note that there is good agreement with the results. Eventually, the use of CFD to simulate flow is validated [7]. This is also illustrated when steady-state analysis was performed for inspiratory flow on the entire nasal cavity with normal resting breathing rates taken as boundary conditions at the inlet and outlet of the model. Note that analysis was performed on a virtual post-surgery model and another model generated directly from the CT scans of the same patient having undergone surgery. It was concluded that even with the limitations presented by using CFD to predict such, results from both models showed reasonable correlation [14]. Using this numerical approach, medical practitioners

can develop effective surgery protocol and design drug delivery devices, while gaining deeper insight into physical and biological phenomena.

As our results also indicated, normal nasal flow shows over 50% total pressure drop near the inferior turbinate head and wall shear stress, and the vorticity were lower in the turbinate than in the nasal valve region [12]. However, major flow streamlines and velocity distributions in coronal sections may vary among individuals. Surprisingly, on average, more flow passed through the middle than the inferior meatus and correlated with better patency ratings [15]. The pressure gradients within the sinus cavities varied according to their place of connection to the main passage. Alternations in pressure gradients induced a slight pumping phenomenon close to the ostia, but no movement of air was observed within the sinus cavities [8].

Nasal septum deviation (NSD) is the most common aetiology for nasal airway obstruction (NAO), and septoplasty is a very common surgical procedure. Septal deviations are commonly observed during physical examinations, and surgeons face the challenging question of determining if NSD causes NAO in a given patient or not. In addition to NSD, one may encounter inferior turbinate hypertrophy and/or nasal valve insufficiency in the patient; thus, septoplasty is often recommended with turbinate and/or nasal valve surgery. Quantitative criteria are rarely adopted to select patients for surgery, which may explain why up to 50% of patients report persistent or recurrent symptoms of nasal obstruction postoperatively [16]. Personalized nasal surgery with numerical simulation of respiration enabled otorhinolaryngologists to understand, estimate and define the possible role of the procedure for an individual with NAO.

We would also like to outline some of the limitations that CFD presents in this field. CFD is a time-consuming process, taking several hours of work for preparation of 3D models and simulation of surgeries on these models. Additionally, technique usually requires a high-performance multi-core computer, expensive software(s) and aeronautical engineering. Second, translating CFD findings into patient care and clinical practice is a hard task. For doing this, several authors either compared healthy and pathological subjects or compared the same patient before and after the surgical procedure. Alternatively, CFD findings can be correlated with laboratory evaluations as acoustic rhinometry and rhinomanometry which is still difficult to perform on larger scale of subjects [17]. However, postoperative CFD requires a CT scan, and postoperative CT scan is not always justified as it exposes patients to additional radiation [17]. Moreover, calculation and implementation times are still long for daily practice, as stated.

48.5 Conclusion

The 3D nasal airway is simulated using computational fluid dynamics. The real CT images are reconstructed using the commercial medical imaging software. The software is used to generate and refine to adapt high curvature regions. The generated mesh is utilized to perform 3D CFD simulations. The velocity, pressure contours

and streamlines are visualized at different cross sections of the 3D nasal airway. We conclude that CFD provides clinically useful, logically consistent and understandable information that would otherwise be unavailable [18].

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Some Forensic Aspects of the Nasal Septal Deformities

49

Ranko Mladina

49.1 Introduction

The literature data on the forensic aspects of the nasal septal deformities is very scarce. There are two main reasons for that: (1) the absence of an official international classification of the nasal septal deformities and (2) ignorance of the pathophysiological mechanisms of the onset of the particular types of nasal septal deformities and the ancillary changes of the structure of pertaining nasal mucosa, be it anterior to the deformity itself, behind it, or both.

One of the classifications of the nasal septal deformities (1987) defines six main types, whereas the seventh type always presents variable combination of the six previous (Fig. 49.1).

Two out of six types (types 5 and 6) are the most important from the forensic medicine aspect and are presented at Figs. 49.2 and 49.3. Both have been clinically proven as directly, dominantly inherited, thus having nothing to do with whichever type of the force against the subject's nose.

The term "hypertrophic" has been used on purpose since this term automatically makes one to imagine somewhat to be of a bigger size than usual. But, in case of the intermaxillary bone, one should know that this bone has the shape of the letter "Y." During the embryonic life, its lower part is supposed to be intruded and finally integrated between the palatal processes of the left and right maxilla. The final result, immediately after the birth, should be the integration of three separate bones in one: the lower part of the intermaxillary ("Y"-shaped) bone and both palatal processes of the maxilla. Since the maxilla and intermaxillary bone normally, although unexpectedly, grow downward and in the anterior direction (according to Enlow's findings) by the processes of resorption of the bone in the nose and apposition of the new bone over the hard palate and anterior surface of the maxilla, in case of type 6,

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C. Cingi et al. (eds.), *Challenges in Rhinology*,
https://doi.org/10.1007/978-3-030-50899-9_49

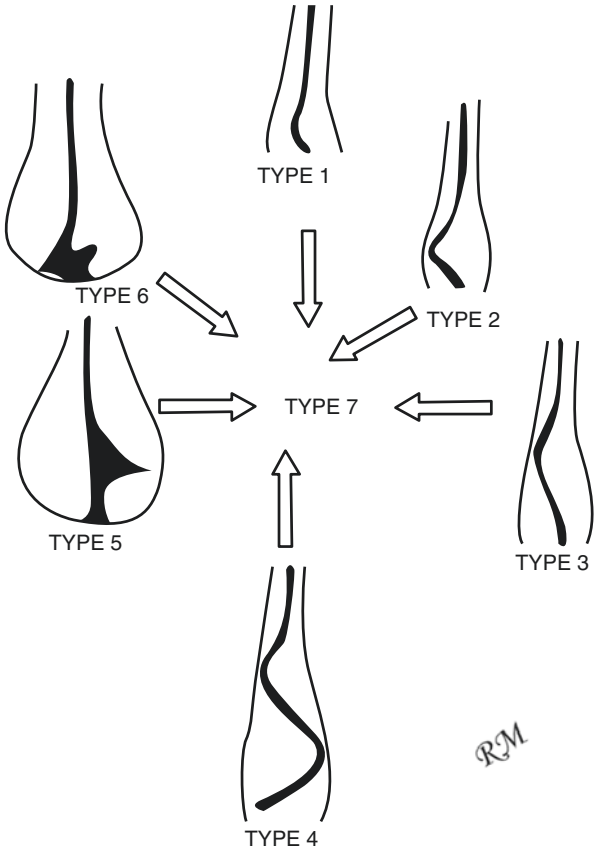

Fig. 49.1 Schematic presentation of nasal septal deformities. Types 5 and 6 have been drawn in an anterior-posterior view, whereas all other types have been drawn in a superior-inferior view

it goes for the hypotrophic, not at all hypertrophic wing of the intermaxillary bone which consequently remains in a higher position than the one which grows normally. The other side of the maxilla is growing normally (that means downward and anteriorly) producing the lowering of the related nasal floor and the other arm of the "Y"-shaped intermaxillary bone. Because of that this bone by time becomes much disfigured letter "Y." Its lower arm enables sliding out of the inferior border of the growing quadrangular cartilaginous septal plate thus promoting the onset of the anteriorly positioned "septal crest" which consists of the bony part (normally growing wing of the intermaxillary bone) and the lowest and most anterior part of the quadrangular, cartilaginous part of the nasal septum. Since the quadrangular plate now stays in an oblique position while the hypotrophic arm of the intermaxillary bone is still sticking laterally, the typical groove between these two anatomical parts develops and crucially determines the type 6 nasal septal deformity. In case presented in Fig. 49.4, it would be recorded as "6L," meaning type 6 with the groove on the left side, as already stated above.

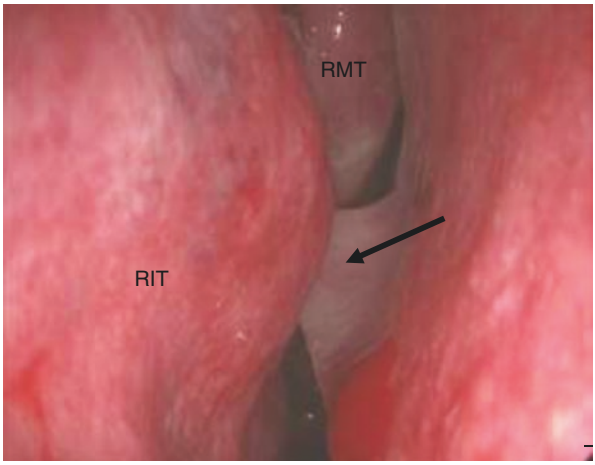

Fig. 49.2 Right-sided type 5 septal deformity (black arrow). The usual endoscopic view of the deepest part of the nasal cavity showing in this very case a right-sided type 5 septal deformity. *RIT* right inferior turbinate, *RMT* right middle turbinate. It goes for a unilateral horizontal deformity, discretely ascending from anterior to posterior, looking like an almost horizontally positioned ancient Turkish saber which juts as more and more lateral as deeper in the nose, resulting in most of the cases in an impaction of its tip to the region of the sphenopalatine foramen

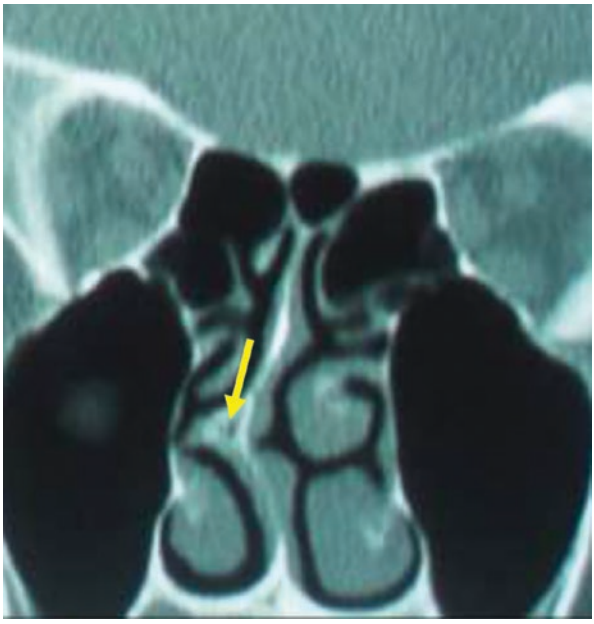

Fig. 49.3 Coronal CT scan presenting the right-sided type 5 septal deformity. The bony connection between the perpendicular lamina, vomer and palatal processes of the maxilla can show the signs of so-called sinus septi nasi (yellow arrow). In everyday practice the surgeon could therefore be faced with some sort of contents during the removal of this very part of the deformity!

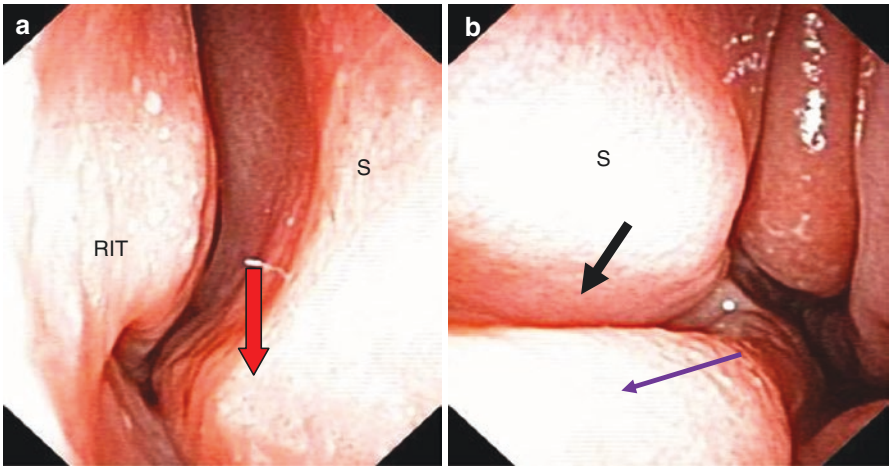

Fig. 49.4 Clinical appearance of the type 6. (**a**) The basal crest in the right nasal cavity (red arrow); *RIT* right inferior turbinate, *S*, nasal septum. (**b**) There is a typical, unique deep groove (black arrow) between the nasal septum (S) and the "hypertrophic" wing of the intermaxillary bone (violet arrow). The groove always strictly determines this type of septal deformity (black arrow) as well as the side of the deformity: in this very case, it goes for the left nasal cavity, or abbreviated as "type 6L"; at the correspondent level of the groove, there is a contralateral crest which is visible on the Fig. (**a**) (red arrow)

Finally, every single type 6 of nasal septal deformities is followed by the expected asymmetry of the hard palate (Figs. 49.4, 49.5, and 49.6), and in very many cases, a bifid uvula can be found during the careful examination of the throat (Fig. 49.7). In addition, in cases of the type 6, the doctor should always palpate the *raphe palati* line (midline of the hard palate) as to check out whether or not there exists any sign of hidden, submucosal cleft of the hard palate.

Since this type of septal deformity, exactly as in cases of type 5, can easily be verified taking a look in the nose of the closest blood relatives of the injured person, this represents the cornerstone for the forensic science and court witnesses practice. It must be emphasized that the particular types of nasal septal deformities in man could slightly differ between each other, but the characteristic feature of the particular type is a backbone that every modern rhinologist and court expert witness should be able to instantly recognize. Besides type 6 which is always located very anteriorly in the nose, generally it is not at all enough to take a look into the nose by means of the nasal speculum (anterior rhinoscopy) and make any "instant" conclusions. The rhinology of today strictly and strongly requires three steps in the examination of the nose, particularly for the court purposes: (1) native anterior rhinoscopy by means of the nasal speculum, (2) anterior rhinoscopy after the correct nasal decongestion applying two puffs of the decongestant spray and waiting for several minutes before the second look into the nose, and (3) nasal endoscopy after the decongestion and superficial local anesthesia of the nasal mucosa.

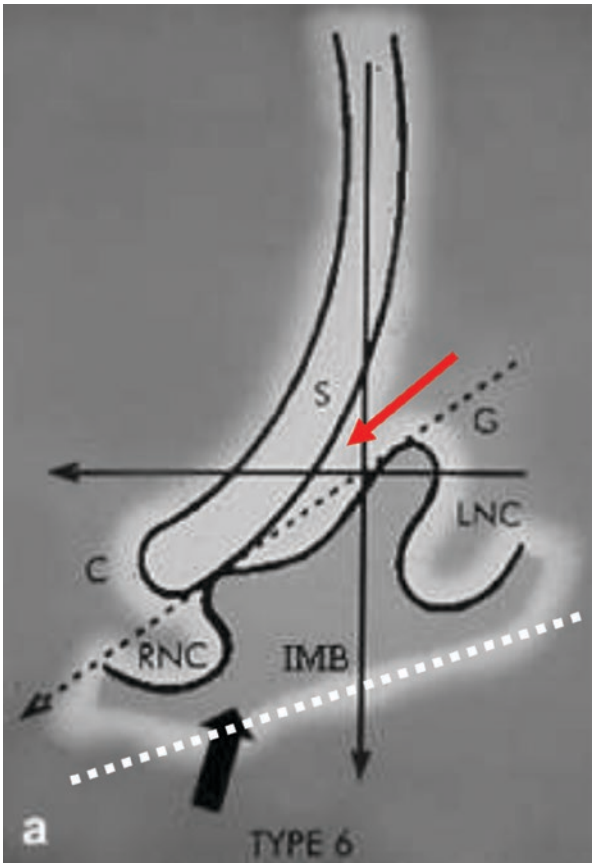

Fig. 49.5 The drawing of the left-sided type 6 septal deformity. The groove is located at the left side (indicated by the red arrow). That is why this particular case was named "left-sided type 6 septal deformity." The side of the groove determines the side of this deformity. *IMB* intermaxillary bone, *RNC* right nasal cavity, *LNC* left nasal cavity, *S* septum (quadrangular cartilaginous plate), *C* crest, *G* the resultant of the forces (dotted arrow) directing the way of the slipping out of the inferior border of the nasal septum. White dotted line shows the asymmetry of the hard palate

Still, not only the tools and most updated equipment are sufficient for the correct examination of the internal nose, but, on the first place, a large theoretical knowledge is essential. That is why in the year 2019 and onward, the classification of the nasal septal deformities is needed for every single rhinologist and court witness in the domain of rhinology.

49.2 The Types of Septal Deformities that Could Be Interesting for Forensic Medicine Since They Are in Rule Related to Force Against the Nose (Types 1 and 2)

Type 1 means a mild, unilateral vertical septal ridge in a valve area which slightly interferes with the function of the nasal valve (*Latin term: limen nasi*); thus in most of the cases, it has a mild clinical importance (Fig. 49.8).

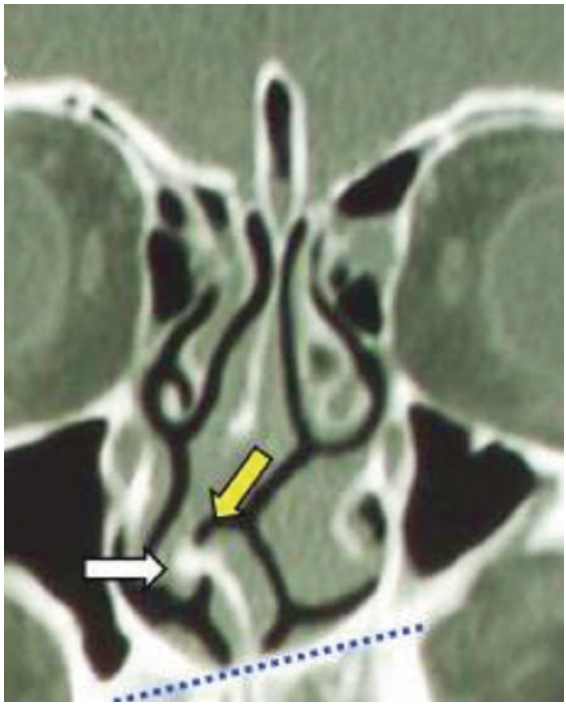

Fig. 49.6 Coronal CT scan of the paranasal sinuses. Septal deformity type 6 is clearly recognizable with typical groove (yellow arrow) and basal crest (white arrow). Dotted blue line shows asymmetry of the nasal floor and hard palate which both are always found in this type of septal deformity

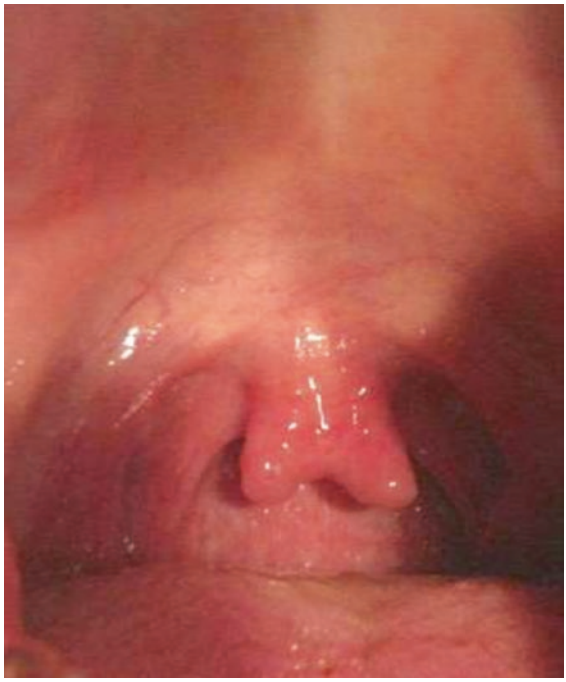

Fig. 49.7 Bifid uvula in a patient carried type 6 septal deformity

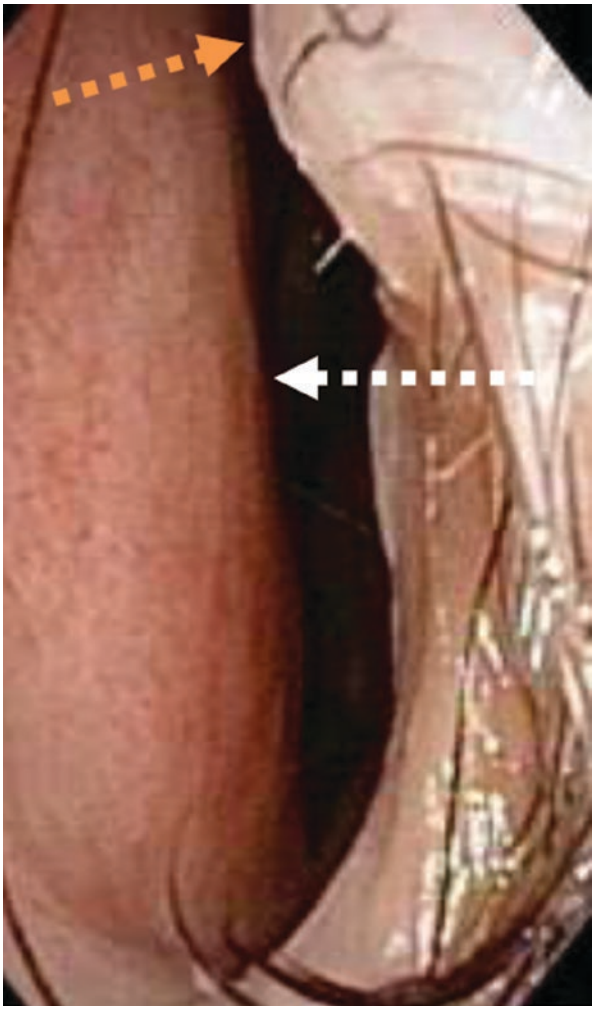

Fig. 49.8 Left-sided type 1 (dotted white arrow). The anterior nasal valve ("limen nasi"): light-brown arrow

Type 2 again means unilateral vertical ridge, but this time much more emphasized than it is the case in Type 1, i.e., it stays in a close contact to the anterior nasal valve (*limen nasi*) and thus, from the physical point of view, remarkably narrows or even totally blocks the air passage on the related nasal side (Figs. 49.9 and 49.10). The normal angle between the nasal septum and the anterior nasal valve (*limen nasi*) should vary within 20–25°. In very many of the cases of the type 2, this angle is diminished to 10° or even less! The final result can be the hypertrophy of the mucosa of the posterior pole of the ipsilateral inferior turbinate (Fig. 49.11). It is generally believed that curly hypertrophy of the nasal mucosa, particularly of the posterior part of both inferior turbinates, evolves because of turbulent-shaped airstream in the nose. The normal inspired airstream is expected to be linear and parabolic in shape.

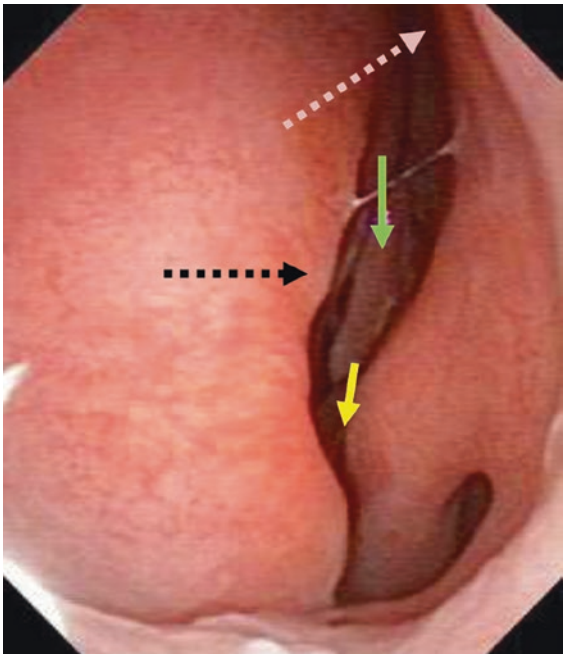

Fig. 49.9 Left-sided moderate septal deformity type 2 (dotted black arrow) that still remarkably narrows the entrance to the left nasal cavity. Still, the inferior turbinate after the proper decongestion of the nasal mucosa can be followed almost to the half way to the choana (yellow arrow). Middle turbinate is thin but still perceivable (green arrow). Rose dotted arrow indicated the line of limen nasi, i.e., the anterior nasal valve

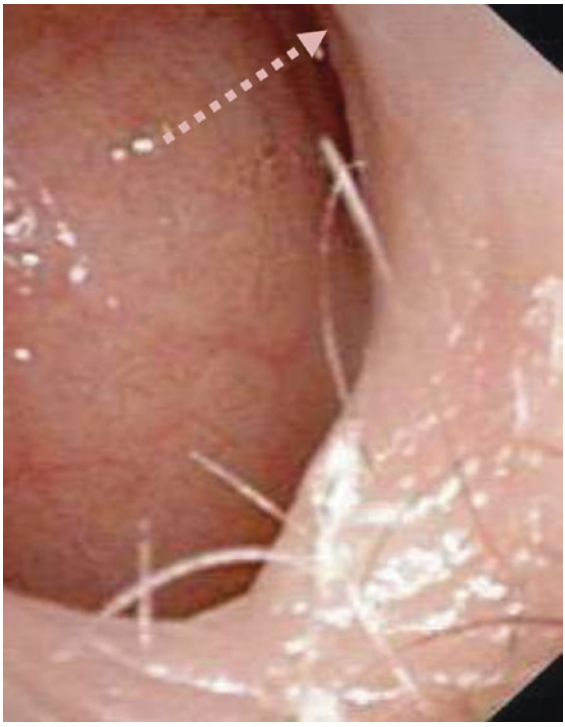

Fig. 49.10 Left-sided septal deformity remarkably narrows the entrance to the left nasal cavity. The inferior turbinate, even after the proper decongestion of the nasal mucosa, cannot be identified. Middle turbinate cannot be seen as well. The angle between the anterior nasal valve (limen nasi—rose dotted arrow) and the septum is practically zero (0°)

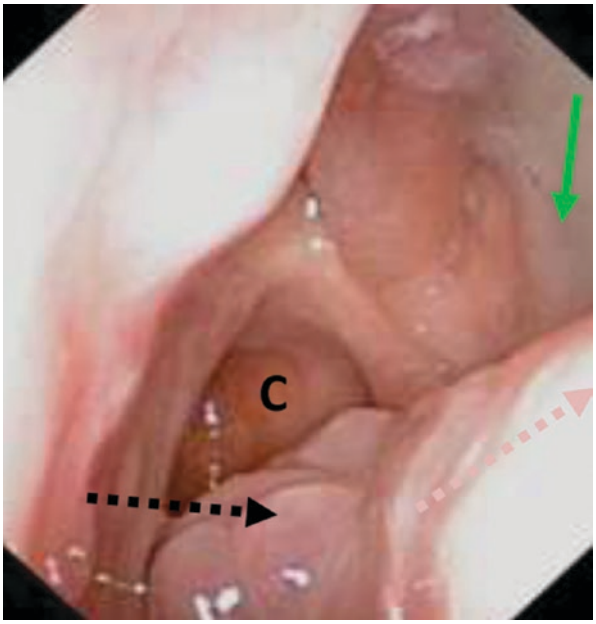

Fig. 49.11 The posterior end of the left inferior turbinate (black arrow) endoscopically shows the signs of curling hypertrophy! The cross-sectional value of the left choana (C) is obviously diminished! In this very case, one should be careful since a slight trace of mucopurulent secretion (green arrow), coming from the middle meatus, is suspected for coexisting THS with the typical melting of the secretion suffix from the recirculating mucus. Melting suffix from the recirculating mucus in cases of two holes syndrome can provoke the curling hypertrophy of the posterior part of the inferior turbinate as well! This can be seen also on Figs. 49.12 and 49.13. Besides, very many cases of chronic otitis media with effusion in children and chronic otitis media in adults have the problem of the Eustachian tube orifice which can easily be covered by hypertrophic mucosa and thus be partly or totally out of function!

If there is any mechanical obstacle for the airstream from nostrils toward the choanae, we can expect at least two physical phenomena:

1. In case of narrow, but still passable, way for the inspired airstream (emphasized type 1 or moderate type 2), the proportional acceleration of the airstream on the narrower side is expected to be elevated according to the mathematical formula for acceleration: $a = \frac{\Delta v}{t}$ where the $\Delta v = a \times t$. In this case the symbol Δ means "delta"; in physics and mathematics, it concerns to the minimal changes, variations in fact; "*a*" symbolizes acceleration itself, "*t*" means the time (*Latin: tempus*), whereas "*v*" means the speed *(Latin: velocitas).*
2. The airstream in the left and right nose is expected to arrive to both choanae at the same time. To achieve this, the speed of the right and left nasal airstream have to be equalized.

The final result is elevated speed of the airstream in the narrower space and diminished speed in the larger one. As to the shape of the airstreams of inspired air,

the one in the narrower space will be more or less linear (but more speedy while passing through the narrow region), and the opposite one will be more turbulent owing to the morphologic wideness and therefore the lack of the resistance (coming usually from the septum and lateral nasal wall). Inspiring both linear, high-speed airstream and the slow, turbulent one shows almost the same result to the nasal mucosa: the conversion of the epithelium from cylindrical, typically respiratory, ciliated epithelium into the multilayer squamous cell one. Furthermore, after passing through the narrow region, the airstream suddenly comes to the wide one (like in all "vertical" septal deformities, i.e., types 1, 2, 3, and 4) and thus also becomes turbulent instead of being linear.

Type 3 means unilateral vertical deformity, i.e., unilateral convexity located in the middle of the nasal cavity, i.e., next to the anterior edge of the head of the middle turbinate (Fig. 49.12).

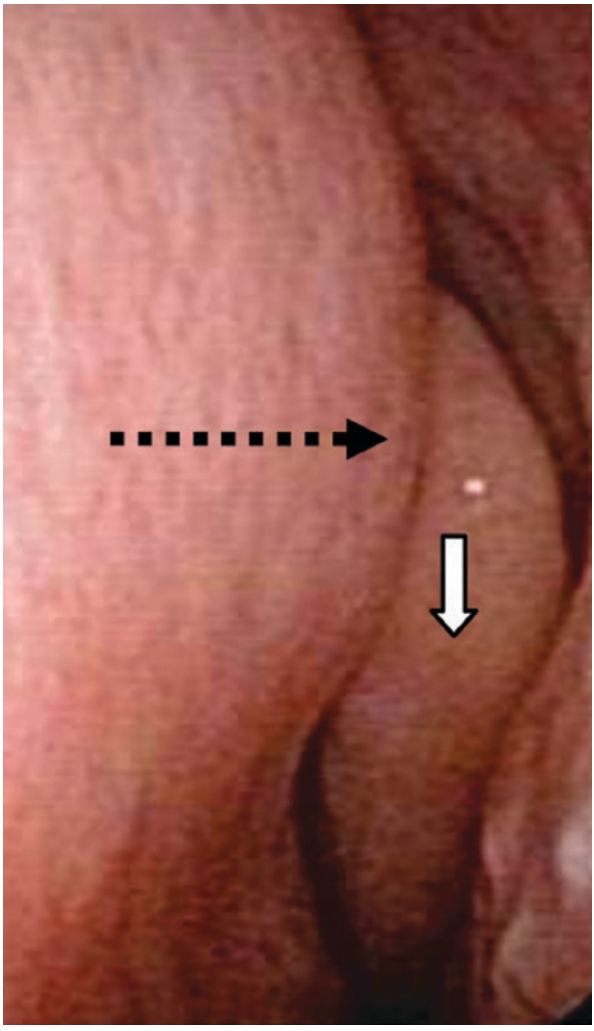

Fig. 49.12 Left-sided type 3 ("septal belly"—black arrow) which in this very case partly disturbs the clear vision to the middle turbinate (white arrow). In some cases the convexity of the middle septal part is so emphasized that the middle turbinate cannot be seen at all, even during the endoscopy after the proper nasal decongestion and superficial anesthesia

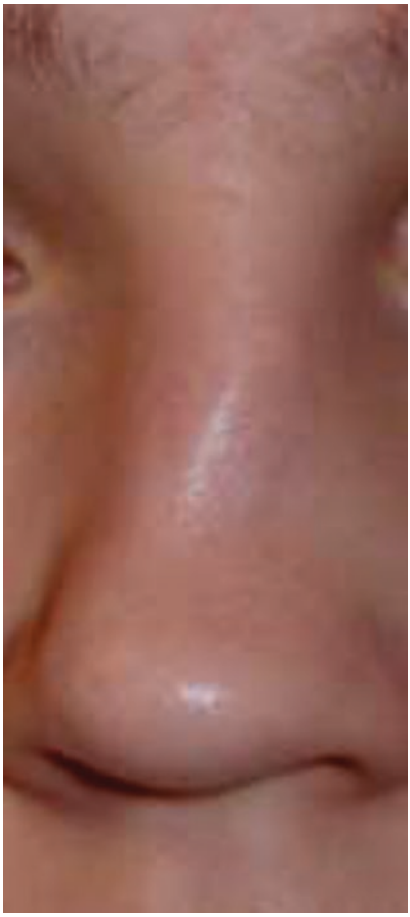

Fig. 49.13 Scoliotic nasal pyramid

The nasal cavity is very narrow on this side and very wide on the opposite one because of the correspondent septal concavity on this side. Type 3 can also be inherited, though the proofs are still to be better scientifically firmly supported. In most of the cases of the type 3, the big question arises on the possible etiology, unless the whole nasal pyramid didn't get a "C-shape" or "reverse C-shape" form just after the trauma against the nose (Fig. 49.13).

It seems, however, that the development of this type has much more to do with some anthropometric values than with the trauma against the nose. In forensic evaluation of this type, one should be very cautious! The reason is that Huxley's angle of the skull base angulation could play a role in cases when its values are less than 130°. In these cases there is a real presumption of a certain degree of pressure to the nasal septum structures from behind (posterior arm of Huxley's angle, in fact the clivus), and this could promote the onset of the type 3 septal deformity. It goes for the unilateral declination of the junction between the perpendicular lamina of the ethmoid bone and the quadrangular cartilaginous septal plate. In short, smaller values of the basomaxillary angle (normal values vary from 130° to 140°) press over

the perpendicular lamina from backward (Fig. 49.14), and there is the collision between it and quadrangular cartilaginous lamina of the nasal septum. Because of that, both the type 3 and the type 7 require latero-lateral and anterior-posterior CT scans of the paranasal sinuses as to be able to measure Huxley's angle and also to check nasal bones in cases when the nasal pyramid is concurrently deformed.

Type 4 is a bilateral vertical deformity (Fig. 49.15), consisting in fact of previously mentioned types, i.e., type 2 at one side and type 3 at the other (so-called "S-shaped" septum, or "reverse S-shaped" septum). From the forensic point of view, the type 2 could be concerned as the consequence of the trauma against the nose, but the type 3 not if there is abovementioned deformation of the external nose in sense of the scoliosis.

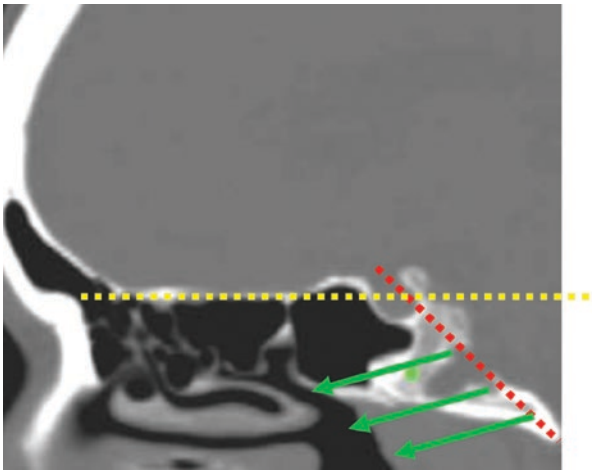

Fig. 49.14 Sagittal CT scan of the human skull. Typical angulation (Huxley's angle) between the anterior (yellow dotted line) and posterior skull base (red dotted line) is obvious. Possible pressure comes from behind (green arrows)

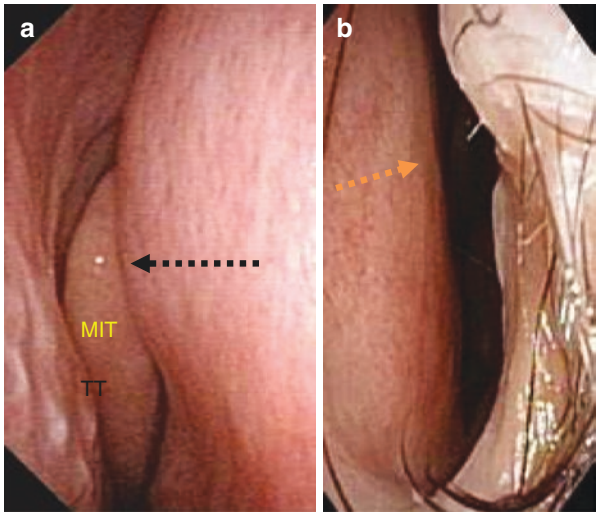

Fig. 49.15 Type 4 nasal septal deformity. (**a**) Right-sided type 3, i.e., convexity of the nasal septum (black arrow) hiding almost half of the anterior pole of the middle turbinate (MIT). They stay in a close contact. (**b**) Left-sided type 1 (light-brown arrow). This is an example of so-called "S-shaped" nasal septum

Type 7 ("crumpled septum") is very variable and presents a combination of previously mentioned types with all their clinical implications. In case it involves type 1, or type 2, or if there is a scoliotic external nose which corresponds with the underlying septal deformity (type 3), all of them could be a matter of forensic considerations.

49.3 Epithelial Changes as a Forensic Proof for the Incriminated Deformity

Epithelial changes of the nasal mucosa can serve as a forensic proof for the connection between the incriminated deformity and the trauma against the nose. One should know that the histological changes of the nasal mucosa epithelium are just a matter of time; since the changes from the typical respiratory epithelium take some time, they simply cannot happen at once. An approximate period of time required for such changes is at least 6 months after the trauma. The most frequent changes are curling hypertrophy of the tail of the inferior turbinate mucosa and the conversion from the typical respiratory ciliated epithelium to the multilayer squamous cell metaplastic epithelium.

There are four practical ways to test these possible changes:

1. Cytological smear
2. Saccharine test
3. Carbon particle
4. Histopathological analysis of the piece of tissue

1. *Cytological smear* examination of the mucosa behind the deformity which is supposed to be of a respiratory type, i.e., cylindrical ciliated epithelium, can show normal respiratory cells or the changes in terms of metaplasia into the squamous cell epithelium. In case the multilayer squamous cell epithelium is found, it means that the trauma took place time ago (at least 6 months ago) or has nothing to do with this finding.

2. and 3. *Saccharine and carbon particle test* should be performed by endoscopic observation of the presumed (or not) movement of these particles toward the nasopharynx owing to the action of the still existing cilia of the typical respiratory epithelium. The time required to get the particles at the level of the choana varies individually, but approximately it takes up to 4 min in case the respiratory epithelium is still there.

4. *Histopathological examination* is a more demanding method, the method of the last choice, since it requires undersigned informed consent from the subject investigated and even his or her undersigned approval which sometimes makes things complicated for the court expert witness and other persons involved in the case (Fig. 49.16).

When considering the epithelial changes of the nasal mucosa, the court expert witness should check endoscopically also whether or not there are any clinical signs

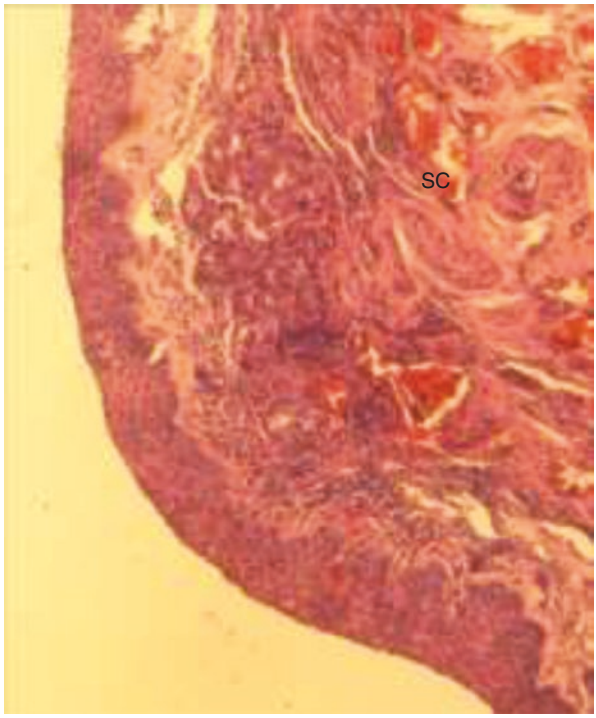

Fig. 49.16 The right-sided type 3. Histological picture of the piece of septal mucosa taken from the narrowest part of the nasal cavity, just opposite to the head of the middle turbinate (*SC* septal convexity). The epithelium shows typical appearance of the squamous cell metaplasia

of THS (two holes syndrome) and also use a CT analysis; otherwise he or she can't be sure what exactly is the reason for the squamous cell metaplasia of the otherwise presumed respiratory mucosa, particularly in the posterior half of the nasal cavity. Pathohistological microscopic examination of the mucosa behind the deformity (which is supposed to be of a respiratory type, i.e., cylindrical ciliated epithelium) might present the multilayer squamous cell epithelium instead which could mean, as in case of cytological smear mentioned above, that the trauma took place time ago (more than 6 months ago) or has nothing to do with this finding.

49.4 Discussion

To be familiar with classification of nasal septal deformities helps enormously in the situation when an ENT specialist is asked as a court expert witness to give an expertise on whether or not the certain nasal pyramid or nasal septal deformity or both are connected to the incriminated trauma against someone's nose.

There is no doubt about the genesis of the types 5 and 6, since they have been scientifically proven as directly inherited septal deformities. As a proof for the judge, for the members of the jury and/or, in complex cases, even the members of the court chamber, an endoscopic examination of the victim's nose could be transmitted in the real time to the screen in the courtroom, as to clearly demonstrate the

shape of the nasal septum of the victim and his or her closest relatives. There is no way to fail in successfully representing the existence of the same type of the nasal septal deformity in the victim and the closest relatives.

One issue, however, should be kept in mind prior to the demonstration: the side of the deformity and its intensity are not the matter to be inherited, but the typical shape absolutely is!

The nasal septal deformities that could be related to the trauma against the nose are those with the "vertical" deflection like types 1 and 2. Types 1 and 2 differ only regarding the intensity; otherwise they are almost identical. These two types are characterized by the deflection of the cartilaginous septum (anterior part of the quadrangular plate) in the closest neighborhood of the anterior nasal valve (*limen nasi*). There are two main types of the deflection of the septal cartilage in types 1 and 2. They differ from the histological aspect like it could be seen in Fig. 49.17a, b, as well as in Fig. 49.18.

These histological findings, however, have no big influence on the decisions of the court expert witness since he or she is invited to the court to give the opinion which does not include the post-traumatic intraoperative neither histological findings. In most of the cases, the incriminated trauma against the nose happened time ago; therefore even the connective tissue envelope around the fracture line can be easily identified during the surgery. All experienced and skilled nasal surgeons know these facts very well.

In general, type 1 and particularly type 2 can be connected to the trauma against the nose particularly if it has come from the anterior-posterior direction or, rarely,

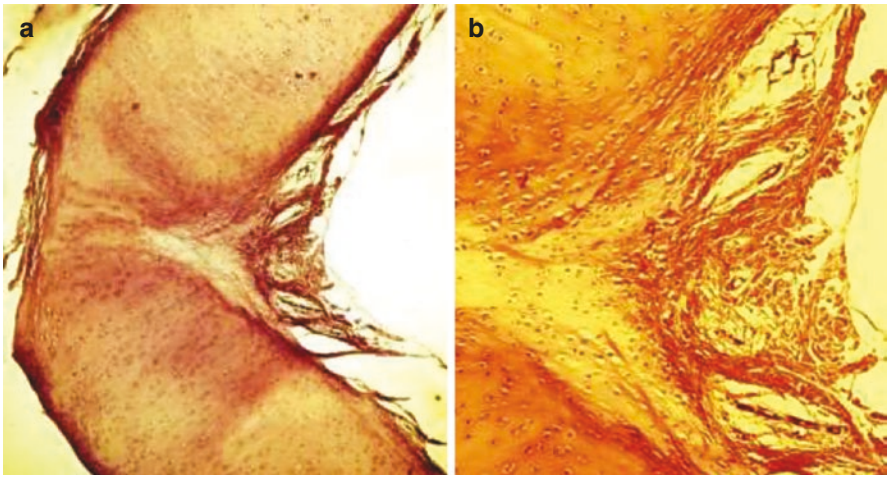

Fig. 49.17 (**a**, **b**) Histology of the septal cartilage (horizontal section!) through the right-sided type 2 septal deformity of an adult patient. Despite an emphasized angulation, there are no signs of discontinuity of the cartilage. (**b**) A close-up view of the angulation shows typical appearance of so-called green stick fracture, i.e., no tissue discontinuity (no gap), and the high amount of chondrocytes can be clearly seen invading the damaged place

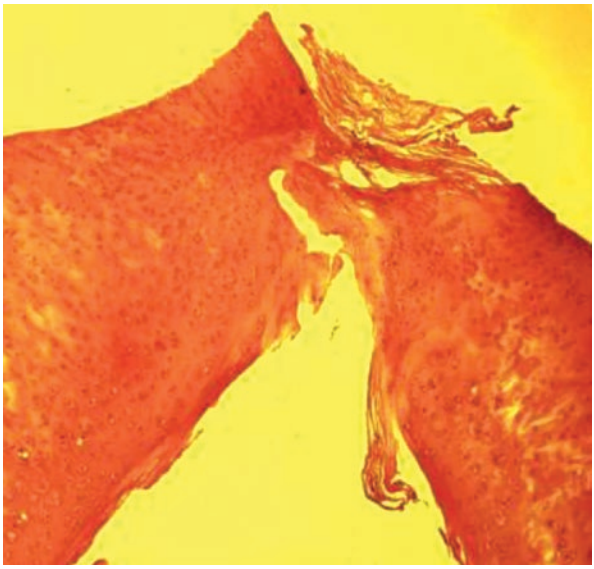

Fig. 49.18 Histological appearance of the obvious discontinuity of the septal cartilage after the serious trauma against the nose

from the latero-lateral direction (fistfighting, sports, or traffic accidents, for instance). In cases of lateral-lateral direction, nasal septal deformities type 1 or 2 are always located at the opposite side of the side from which the punch came. That is why in cases of left-sided type 2, the punch most probably came from the victim's right side, which, in addition, suggests that the assailant most probably was a left-handed person. This fact could sometimes help the police detectives to narrow the circle of the suspicious assailants.

As to the type 4, the court expert witnesses should bear in mind that this type can also be considered as a consequence of the trauma against the nose, but only partly since it consists of type 3 at one side and type 2 on the opposite side. Type 3 has been excluded as a deformity of the traumatic origin unless there are no obvious proofs of the fracture of the nasal bones (scoliosis of the nasal pyramid) whose appearance corresponds with this type of nasal septal deformity (Fig. 49.13).

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