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Meet the editor

Dr Tang-Chuan Wang is an excellent otolaryngologist – head and neck surgeon in Taiwan. He is also a research scholar of Harvard Medical School and the University of Iowa Hospitals. During his Fulbright experience, he worked in the Hospital of the University of Pennsylvania, Boston Children's Hospital, and Massachusetts Eye and Ear. He is not only working hard on clinical and basic medicine but also launching out into public health in Taiwan. In recent years, he has devoted himself to innovation. He always says that "in theoretical or practical aspects, no innovation is a step backward". Due to his contribution to biomedical engineering, he was invited onto the executive committee of HIWIN-CMU Joint R & D Center in Taiwan.

Contents

Preface

Management of paranasal sinus disorders is not only a test of knowledge but it is also an art form. Great progress has been made on endoscopic sinus surgery in recent decades and this technique lets us look into the remote corners of sinuses. However, we still have a lot of challenging issues, such as frontal sinus, sinus lifting, and sinonasal cancers. The only way to solve these problems is to face them. Based on these concepts, this book incorporates new clinical and research developments as well as future perspectives in the ever-expanding field of rhinology. The book is a comprehensive reference for ENT residents and practicing otolaryngologists who wish to expand their expertise, develop a broader armamentarium of techniques, and successfully manage their patients with sinonasal disorders.

In this book, there are sections on the challenges of today, such as the development of frontal sinuses, complications of sinus augmentation, managements of rhinosinusitis and sinonasal Neoplasms. I hope this book helps readers explore the mystery of paranasal sinuses.

In the section of the Challenging Issue on Frontal Sinuses, *Dr. Nikolova Silviya et all.* will discuss the frontal bone development and maturation, from the viewpoint of the frontal sinus pneumatization in relation to the metopic craniosynostosis and failed closure of the metopic suture. Furthermore, the persistent metopic suture is frequently associated with a frontal sinus underdevelopment. In the section of Challenging Issue on Sinus Augmentation, *Dr. Sindel Alper et all.* will review the contemporary methods for maxillary sinus augmentation and presents both recommendations for prevention and management of the sinus lifting associated complications. Then *Dr. Atalay Berkem* will present his application of Platelet-rich fibrin (PRF) in sinus augmentation and the clinical and radiological findings that have shown good results regarding new bone formation. In the section of Challenging Issue on Rhinosinusitis and Sinonasal Neoplasms, *Dr. Şentürk Mehmet* will talk about medical management of rhinosinusitis, which includes antibiotics, antihistamines, nasal decongestants, corticosteroids, mucolytics, leukotriene antagonists, and nasal irrigations. Each patient must have the appropriate treatment option selected for them and prescriptions must be tailored according to the patient need. Then *Dr. Mowatt Lizette* will review the epidemiology of orbital cellulitis, pathogenesis, causative organisms, investigations, and treatment. Prognostic factors will be also presented. At the end, *Dr. Sharma Deepti et all.* discusses why the management of sinonasal cancers remains a major challenge in oncology due to highly advanced cancer stage at the time of diagnosis.

I appreciate everyone's contributions to this book. They made great efforts to do it resulting in the success of academic work. I would like to thank Marijana Francetic, the Author Service Manager, and Mirena Calmic, the Commissioning Editor, for their wonderful assistance.

Besides, the technical editors are also indispensable to the uniform format in this book. At last, I am always full of gratitude towards the people that helped me mature, including my family, teachers, and colleagues.

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Section 1

Challenging Issue on Frontal Sinuses

Chapter 1

Relation between Metopic Suture Persistence and Frontal Sinus Development

Silviya Nikolova, Diana Toneva, Ivan Georgiev and Nikolai Lazarov

Additional information is available at the end of the chapter

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Abstract

The frontal bone develops as two halves, which further unite in a single bone by the closure of the mid-sagittal metopic suture, typically by the end of the first postnatal year. The frontal sinus begins to expand into the orbital and vertical plates of the frontal bone postnatally and reaches the level of the *nasion* by the fourth year of age. At this time, the metopic suture is usually entirely closed. However, in the cases of failed closure of the metopic suture, its relationship to the frontal sinus development is still obscure. Here, we review the relevant literature and discuss the frontal bone development and maturation, from the viewpoint of the frontal sinus pneumatization in relation to the metopic craniosynostosis and failed closure of the metopic suture. The peculiar to the metopic skulls frontal bone configuration is rather an expression of the underlying neural mass demands than a consequence of the metopic suture persistence. Furthermore, the persistent metopic suture is frequently associated with a frontal sinus underdevelopment. It seems that the metopic suture does not inhibit the frontal sinus pneumatization itself, but rather both traits are an expression or an aftereffect of a certain condition during the early development.

Keywords: frontal bone, frontal sinus, persistent metopic suture, *metopism*, metopic craniosynostosis

1. Introduction

The different partitions and layers of the frontal bone develop and maturate simultaneously, but independently from one another in accordance with the functional demands of the related soft tissues/cavities [1]. It has been observed that in cases of persistent metopic suture (MS), the frontal sinus (FS) develops separately on either side of the suture, as well as the MS precludes

the likelihood of development of the sinus beyond the median plane [2–4]. Nevertheless, the supposed influence of *metopism* on the FS development has not been synonymous. Some authors did not find a significant correlation between *metopism* and the underdevelopment of the FS [5–8], which leads to the assertion that the association of these variations is rather random. Other studies, however, revealed a tendency of MS persistence to be significantly related to the FS underdevelopment, including both FS aplasia and hypoplasia [4, 9–14]. Both the MS persistence and FS underdevelopment are not exceptional variations, but the correlation between them is intricate. There are many congenital disorders characterized by an underdevelopment of the nasomaxillary complex accompanied with diminished pneumatization of the FS such as Hajdu-Cheney syndrome, Down syndrome (DS), cleidocranial dysostosis and pyknodysostosis [11], which also feature a preservation of the MS [15–17]. In healthy adults, this correlation is still misunderstood. An adequate assessment of the relation between the frontal sinus development and metopic suture persistence requires a precise study of the events during their formation, development and maturation. In this study, we review the extant literature and discuss the frontal bone development and maturation, from the viewpoint of the frontal sinus pneumatization in relation to the metopic craniosynostosis and failed closure of the metopic suture. We aimed to reveal the possible underlying factors causing a delayed MS closure along with FS underdevelopment.

2. Frontal bone as a functional unit

The functional matrix concept of Moss [1, 18] considers the adult human frontal bone as a single morphological structure, which by no means is a single functional unit. In fact, the form of the frontal bone accurately reflects the functional demands of the protected and supported soft tissues/cavities. Furthermore, each of the three bone layers is functionally independent and responds to different functional demands. The inner table of the frontal bone is functionally associated with the development of the frontal lobe of the cerebral cortex and is exquisitely sensitive to alterations in the cerebral morphology throughout life [18]. The intimate dependence of endocranial form upon the state of adjacent soft tissues could be traced in examples like an extensive compensatory pneumatization and inward displacement of the frontal endocranial plate followed by an atrophy of the frontal cerebral lobe/cerebral hemiatrophy [18, 19]. The differentiation of the outer table is correlated with the increasing demands of the scalp tissues in general and of calvarial muscles in particular [1, 20], as well as with the growing nasomaxillary facial complex [11]. The diploë has several simultaneous functions, including hematopoiesis, weight reduction and pneumatization, functionally responsive to the respiratory system. Even the MS is far from being a simple, intrinsically regulated entity, being greatly influenced by related soft tissues, dura and cranial base [18].

3. Frontal sinus

3.1. Anatomy and development

The FS is one of the four paranasal sinuses and represents a space of variable shape and size between the inner and outer tables of the frontal bone. In adults, the FS appears as two

irregularly shaped cavities separated from each other by a thin septum commonly deviated from the mid-sagittal plane. Usually, the FS lobes extend vertically upwards into the frontal bone squama, but could also expand horizontally backwards between the two tables of the orbital plate [21] and sometimes into the crista galli of the ethmoid bone [11]. Not infrequently, the FS does not invade far into the vertical portion, but grows extensively into the horizontal one and forms large air spaces over the orbits [2]. In cases of the so-called ethmofrontal, orbital or infantile FS [2], it adheres closely to the ethmoidal labyrinth and extends only into the horizontal portion of the frontal bone. In rare cases, the pneumatization could be so profuse to extend beyond the frontal bone into the lesser and greater wings of the sphenoid, the parietal, the temporal, the nasal bone and even into the frontal process of the maxilla [11]. Furthermore, many other variations such as single midline sinus, due to a lack of septum, or supernumerary septa forming additional chambers in a variable pattern, have been reported [2, 11, 22].

Unlike the other sinuses, the FS is practically absent at birth. It could be recognized during the fourth fetal month as diverticula from the lateral nasal wall following the development of the frontal recess. The FS may also arise from the laterally placed anterior ethmoidal cells, the anterior part of the frontal recess or from the frontal furrow [23], but does not pneumatize the frontal bone until the postnatal period. The pneumatization begins in the horizontal (orbital) plate during the first year of life, whereas the pneumatization of the vertical plate commences during the latter half of the second postnatal year and progresses slowly to reach the level of the *nasion* by the fourth year of age [11]. Both lobes of the FS develop independently, and therefore they are often highly asymmetrical due to more rapid pneumatization on one side at the expense of the other [21]. The main period of enlargement coincides with the pubertal growth spurt, but may go on increasing into the fourth decade of life [24].

From the viewpoint of the functional matrix concept, the FS develops through resorption of the diploë, which is housed between the two functionally independent bone tables. The internal table is the intrinsic part of the cerebral capsule, since its periosteum is the outer layer of the dura and is functionally related to the configuration of the frontal lobes. The outer table is related with the increasing demands of the scalp tissues, calvarial muscles [1] and nasomaxillary facial complex [11]. During the first few years of life, the inner table drifts anteriorly in response to the growing frontal lobes. Since there is no significant diploë at this time, the inner table carries the contiguous outer table along with it. After the frontal lobes have undergone their major development at the age of 6–7 years, growing of the inner table ceases and adopts the general shape of the brain. However, the functionally independent outer table continues to drift anteriorly in response to the stimulus of the growing nasomaxillary facial complex, which during puberty is intensively remodeled and displaced more anteriorly and inferiorly. This results in a progressive separation of both tables of the frontal bone, resorption of the diploë and formation of the FS cavities [11].

3.2. Function

Currently, the insight into the biological and functional significance of the paranasal sinuses is speculative rather than known. It has been suggested that the FS contributes to the ventilation and air-conditioning (heating and humidifying the inspired air), the increase in the olfactory membrane area, the lightening of the skull, voice resonance, protection and thermal insulation of the cerebrum and orbits, shock absorption, an adjustment to the growth and development of the cranium. Finally, the FS has been supposed to be an evolutionary residual space [25, 26].

3.3. Factors affecting the FS development and morphology

The factors modifying the FS development and morphology are heterogeneous and are of genetic, environmental or pathological origin. Factors related to the final shaping of the FS and responsible for the wide variations are supposed to be a craniofacial configuration, frontal bone thickness, extent of the supraorbital ridges [27], hormonal growth factors, *metopism*, [11], sex [28, 29], cranial indices and ancestry [30], climatic factors [26, 28, 31], a varying degree of resorption of the diploë, an ambient air pressure and breathing [32]. According to Arnaud et al. [33], both craniofacial configuration and frontal bone width related to the intracranial pressure influence the frontal pneumatization. Heterogeneous pathological condition such as trauma, infection, tumors, mucoceles and various congenital disorders have also been reported as factors affecting the frontal sinus size and morphology in a different way [11].

3.4. FS aplasia

The FS is topographically ethmoidal before it becomes a frontal through pneumatization of the frontal bone, and in this way, it is conspicuously present at birth in all cases [2]. A total agenesis of the FS or the lack of any pneumatization of the frontal bone in healthy adults is very rare [2, 21]. The FS aplasia has been reported to vary from 0.7 to 62% in different population groups [4, 21, 23, 28, 31, 34–39]. The unilateral aplasia of the FS has been found to be more common than the considerably rarer bilateral one [4, 21, 40]. The side prevalence varies in different population groups, but right-sided aplasia seems to be more frequent [4, 8, 21]. There have also been reported cases of agenetic FS, where the contralateral sinus expands and crosses the midline towards the agenetic side and mimics the presence of bilateral frontal sinuses [41]. Sex differences in the frequency of the FS aplasia have been established as well and it tends to be more common in females [21, 35, 38].

3.5. Relation between FS development and definite pathological conditions

Abnormal pneumatization of the FS has been a concomitant finding in a number of heterogeneous disorders. It has been noted that in patients with cerebral hypoplasia, the FS is larger in size while in hypoplasia of the midface, it is smaller [11].

3.5.1. FS hyperpneumatization

The etiology of an excessive sinus aeration and growth resulting in a condition known as "pneumosinus dilatans" is unclear [42]. Pneumosinus dilatans is a generalized or partial enlargement of the paranasal sinuses containing only air. Pneumosinus dilatans occurs as an idiopathic disorder as well as in association with other disorders, including cerebral hemiatrophy [19]. Furthermore, the extreme sinus pneumatization has been associated with heterogeneous disorders such as osteogenesis imperfecta tarda, Turner syndrome, Klinefelter syndrome and acromegaly [11].

3.5.2. FS underdevelopment

The *FS underdevelopment* usually occurs in patients with craniofacial abnormalities. There are many congenital disorders characterized by an underdevelopment of the nasomaxillary

complex. According to Shapiro and Schorr [11], the hypoplasia of the midface blocks one of the major stimuli for the FS pneumatization, i.e. the need to provide a structural bridge between the cranium and the face. Such disorders like Hajdu-Cheney syndrome, cleidocranial dysostosis and pyknodysostosis exhibit diminished pneumatization of the FS [11, 43] and also feature a preservation of the MS [15–17]. Aplasia/hypoplasia of the FS has also been associated with Down syndrome, Apert syndrome, maxillofacial dysplasia, osteodysplasia (Melnick-Needles), Treacher-Collins syndrome [11], cystic fibrosis [44], etc.

3.6. FS in forensic medicine for identification in medico-legal cases

The FS has been considered to be unique in each person [45, 46]. Its shape differs significantly even in monozygotic twins [47]. Being an internal skull structure between the plates of the frontal bone, the FS is well protected from injuries and taphonomic processes. Thus, due to its uniqueness, relatively constant morphology, protected location and frequent radiological documentation, the FS is particularly useful for the identification of human remains [48–52]. The FS has also been used as a feature for sex prediction [53].

3.7. Neurosurgery and endoscopic surgery

The FS morphology has an impact in neurosurgical and endoscopic nasal interventions because of its proximity to the orbit and the anterior cranial base [41, 54]. The possibility to identify the internally located FS through superficial anatomical landmarks is essential for neurosurgery to avoid injury of the FS during intervention, which could lead to postoperative complications [54].

3.8. Methods for FS investigation

As an internal skull structure, the FS has been investigated using different destructive and non-destructive methods with specific advantages and shortcomings which are briefly considered. It has to be noted that when comparing data of the FS agenesis, development, morphology and morphometry, the examining techniques and equipment should be carefully taken into account.

3.8.1. Destructive methods

The FS has been investigated directly through sectioning of dry macerated skulls [7, 55] or by cadaveric dissections [2, 41, 54, 56]. These approaches are applicable for FS investigation on osteological material and in forensic aspect in medico-legal cases.

3.8.2. Non-destructive methods

3.8.2.1. Transillumination

It is the technique of illumination by the transmission of light through a sample/body part. Transillimination of the FS with electric lamp and permanent mapping of its outlines by drawing of the illuminated area with a pencil has been used for FS investigation and measurement in healthy living persons, patients with chronic suppuration, cadavers and macerated skulls in the beginning of the twentieth century [21]. The method has many limitations and is not widely used thereafter.

3.8.2.2. Radiological investigation

With the discovery of the X-rays in 1895 by Wilhelm Röntgen and the subsequent fast development of the radiography, computed tomography (CT) and their application in the clinical practice, the non-invasive diagnostic has been significantly improved. *Radiography (projectional radiography)* is an imaging technique using X-rays to visualize the internal structure of an object. Basically, a beam of X-rays, produced by an X-ray generator, is transmitted through the specimen. The X-rays are absorbed in different amounts by the object they pass through, depending on its density and composition. The unabsorbed X-rays, passed through the object, are recorded on an X-ray sensitive film or a digital detector. The first radiographic signs of FS development are detected between the ages of 4 and 11, with an average of 8.3 years [57]. It is well known that the investigation of a complex 3D structure like FS on 2D radiographs has some inherent limitations. The superimposition of anatomical structures beyond the plain of interest complicates the interpretation of the FS morphology. Furthermore, the estimation of the FS depth, area and volume is complicated and rude [50]. In radiograph-based measurements of the FS, the magnification, positioning and angulation of the skull are crucial for a reliable morphometry [4, 58]. Therefore, in radiographic FS investigations, a definite head/skull orientation is indispensable. Caldwell's view is recommendable, since it provides the clearest FS silhouette and the least chance for error in the interpretation [22]. In Caldwell's view, the skull is inclined 20° from the Frankfurt horizontal plane (FH), the one determined by both landmarks of *porion* and the left *orbitale*. An inclination of 45° from the FH or the so-called Waters' view is also acceptable, but a little bit incorrect for FS measurements [58]. On the plain radiography, the orbital pneumatization is hardly recognizable and is commonly reported as FS aplasia, which unavoidably increases the frequency of FS agenesis [30]. *Conventional plain radiography* has been widely used for FS investigation due to its accessibility. Until now, the conventional plain radiography has been used as a frequent method for diagnostic imaging and documentation of the head including the dentition. Thus, many investigations of the FS in different contexts have been carried out on such datasets of patients' archives. The conventional plain radiography has also been purposefully used for FS investigation on osteological material [26, 30]. In *digital radiography*, the X-ray film/plaque is replaced by a digital X-ray detector. Digital radiography performed on industrial CT systems has been termed an *industrial digital radiography*. Its application as a modality for FS investigation and morphometry in dry skulls has been discussed by Nikolova et al. [4, 14, 58]. Industrial digital radiography allows a precise orientation at the appropriated position, a real-time inspection with optimal X-ray parameters and storage of the captured projections in image file formats. The high resolution of the flat panel detector ensures perfect image quality, precise scaling of the pixel size and reliable readings of the linear FS measurements (**Figure 1**).

3.8.2.3. Volumetric imaging (3D)

It has many advantages and enables the examination of the inner structure of the scanned object into the three orthogonal plains. The volumetric imaging allows the selection of a definite structure as a "region of interest" and its further segmentation. After segmentation,

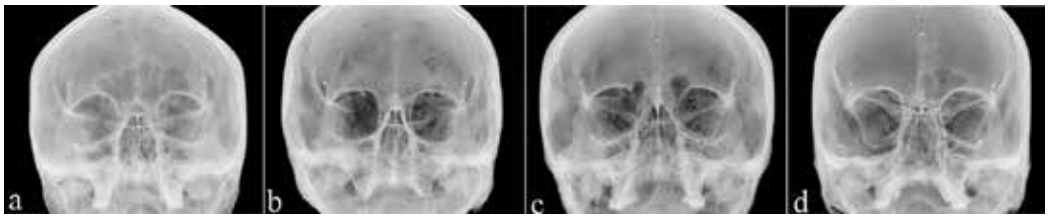

Figure 1. Industrial digital radiographs of dry adult male skulls oriented in Caldwell's view: (a) frontal sinus of normal size; (b) bilateral aplasia of the frontal sinus; (c) underdeveloped frontal sinus of the orbital type in a metopic skull; and (d) right-sided frontal sinus aplasia in a metopic skull.

a representation of the FS cavities could be generated as a separate 3D object, the so-called virtual endocast (**Figure 2**). The virtual endocasts ensure precise metric analyses, storage and further verification of the obtained results, as well as visualization of the real object by 3D printing (**Figure 3**). However, both the resolution and segmentation algorithm are essential for the endocasts reliability (**Figure 4**). In principle, medical and industrial CT systems use different scanning process and algorithms for the calculation and reconstruction

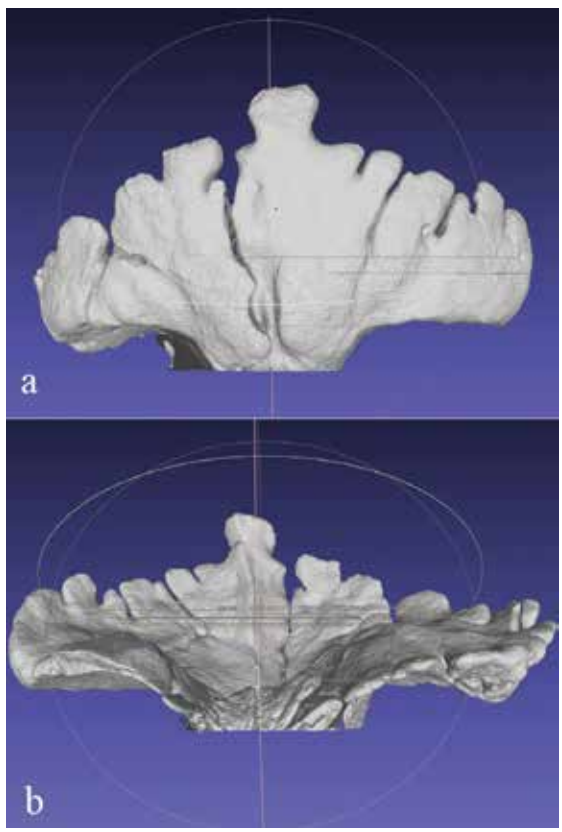

Figure 2. Virtual endocast of the hyperpneumatized frontal sinus segmented from an industrial μCT dataset above the *nasion*: (a) frontal view and (b) backward view.

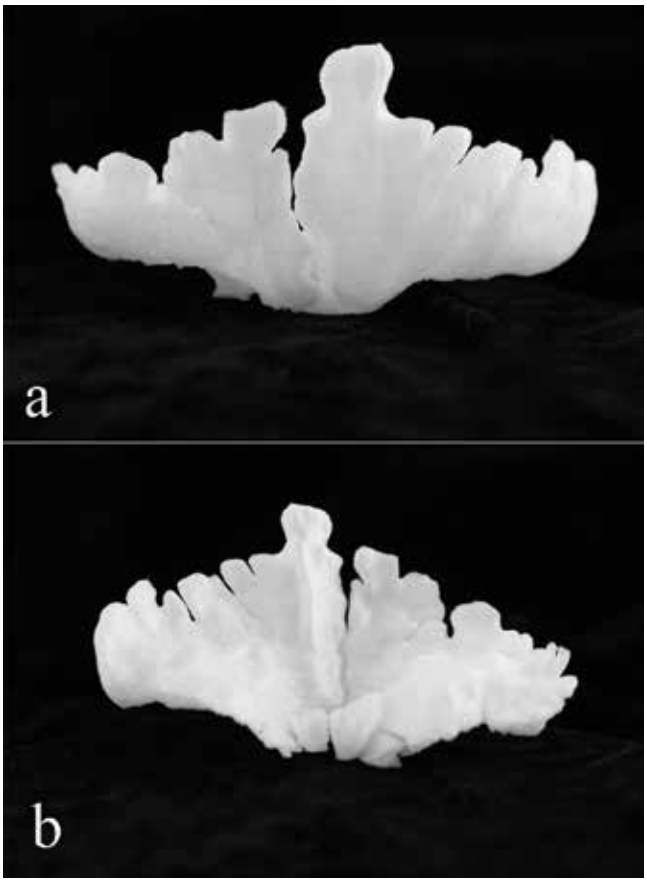

Figure 3. A 3D printed representation of the same hyperpneumatized frontal sinus in real size: (a) frontal view and (b) backward view.

of the volume of the object. Both types of CT systems have their advantages and limitations. For instance, medical CT systems are able to perform fast scan of a large object such as the human body. Limitations are the short exposure time with minimal radiation doses; hence, the images have relatively low resolution. On the other hand, the diagnostic imaging of patients enables the accumulation of large databases which could be used for various investigations on the contemporary populations. Industrial μCT systems are highly versatile and generate images with a high resolution, which allow qualitative observation [59] and quantitative calculation of stereological parameters and degree of anisotropy for porous materials like bone tissue directly from the datasets [60]. Besides, the virtual endocasts of the FS generated from μCT data are very reliable. However, the dimensions of the scan object are too limited, the generated files are large and the modality is entirely inapplicable *in vivo*.

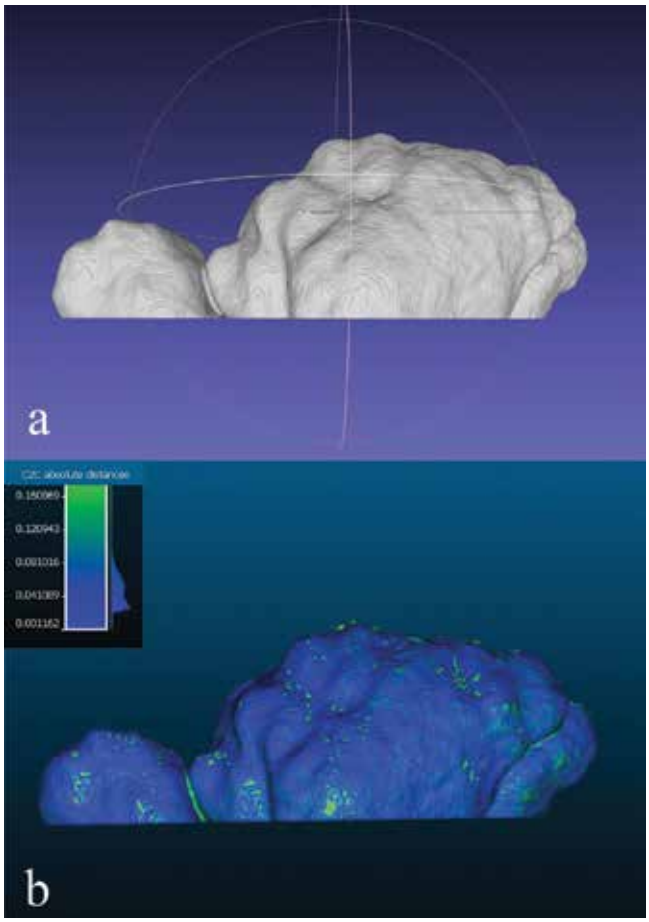

Figure 4. Comparison of frontal sinus virtual endocasts for the establishment of their reliability: (a) virtual endocast and (b) superimposition of two virtual endocasts of the same frontal sinus.

4. Metopic suture, metopic craniosynostosis and *metopism*, definitions and causative factors

The MS is considered an anterior continuation of the sagittal suture. It runs from *nasion* to the anterior border of the anterior fontanelle and is responsible for the growth of the anterior part of the calvaria in width. During the fetal life, the frontal bones undergo intramembranous ossification from a single primary centre located in each halve. The halves are separated by the sutural space [61]. At the ninth gestational week, a small ossification centre is visible in the middle of each supraorbital part of the frontal bones, and subsequently the ossification spreads. The frontal bones reach the midline at the nasal area at the 11th gestational week. The

gap between the two frontal bones in the midline starts closing from the nasal region at around the 16th intrauterine week and moves superiorly towards the anterior fontanelle by the 28th week. At the 32nd week of gestation, there is apparent closure of the MS at the supranasal region, and subsequently, the closure moves superiorly towards the anterior fontanelle [62].

The metopic sutural area, i.e. the adjacent frontal bone edges along with the intervening soft tissues, tends to have a simple "butt-ended" appearance. The interdigitation is a secondary response to imposed biomechanical extrinsic forces [63] and does not follow any special pattern [61], but its widespread presence suggests that the suture is under increased biomechanical stimulation [64]. Some of the interdigitations are united by thin bridges of chondroid tissue which pass through the sutural space, constituting the first microscopic sign of frontal fusion [61]. The location of the fusion point is not invariably endocranial as it is in rats [65], but is sparse and randomly distributed [61].

The MS is the first one to close physiologically as its fusion is a progressive process initiated at the nasion and completed at the anterior fontanelle [62, 66, 67]. The completion of normal fusion occurs between 2 and 14 months in 95% of the normal population with an estimated average age of completion at 8.24 months [68]. After the initiation at an average of 5 months, the process of fusion takes approximately 3–4 months to complete. Furthermore, when the fusion process starts at a younger age, it takes less time to complete [68]. However, the MS has been reported to remain patent up to the seventh year [69].

Premature closure of the MS, metopic craniosynostosis, results in a growth restriction of the frontal bones which leads to a skull deformation known as trigonocephaly [70]. The epidemiology of metopic synostosis has been reported to be 1:5200 newborns, and it is the second most frequently seen type of isolated craniosynostosis after the sagittal one [70]. The etiology of metopic synostosis is multifactorial and has been supposed to be related to intrinsic bone malformation occurred either by genetic, metabolic, or pharmaceutical means [70]. According to Moss [1], the calvaria, dura and cranial base form a single biomechanical entity, and a primary malformation of the cranial base produces abnormal forces within its attached dural fiber tracts, which, in turn, produces premature cranial synostosis. In this sense, the observed neurocranial deformation is the final result. Premature synostosis of the MS, for instance, has been found to be a frequent characteristic of the cleft-palate skull. A cranial base malformation (dysostosis sphenoidalis) was a primary morphological event associated with orofacial clefting. This condition, characterized by a strong basal kyphosis, sets up abnormal tensile condition in the falx cerebri, resulting in the fusion of the overlaying suture [71]. A reported case of trigonocephaly with open MS also suggests that the primary cause is not the MS synostosis, but rather it is a consequence and the underlying cause could be an intrinsic malformation such as hypoplasia of the frontal lobes, which thus require only limited space in the anterior cranial fossa [72]. Furthermore, it has experimentally been established that the normal endocranial fusion of the posterior portion of the MS is well correlated with the structural alterations in the falx cerebri. In rats, normal metopic fusion was inhibited when the underlying dural (falx cerebri) fibre tract was separated from the overlying sutural area. Conversely, periosteal stripping was followed by synostosis of calvarial sutures that normally are patent throughout life [1].

Failed fusion of the MS leads to a condition known as *metopism*. In such cases, the MS runs from *nasion* to *bregma,* the intersection of sagittal and coronal sutures (**Figure 5**). It is

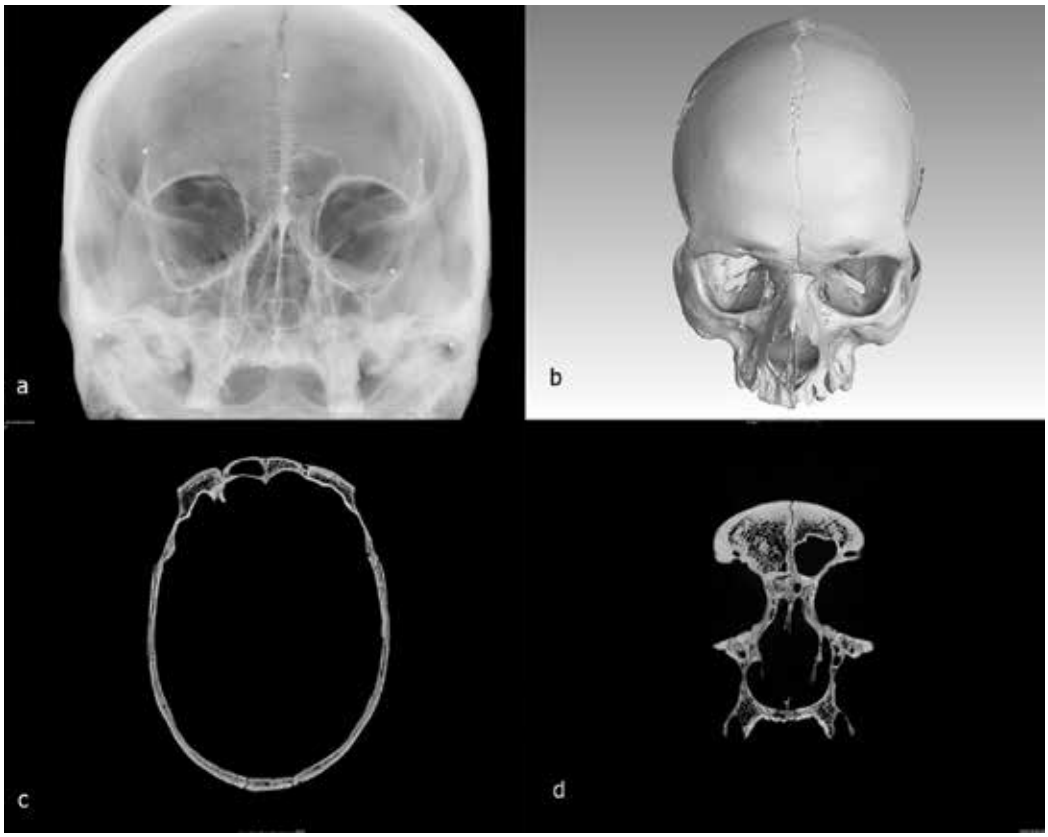

Figure 5. Metopic skull of adult male with aplasia of the right FS: (a) industrial digital radiograph in Caldwell's view; (b) 3D volume representation obtained after scanning with industrial μCT; (c) axial tomogram at the level of FS; and (d) coronal tomogram at the level of FS.

reported that the preserved MS ranges from 0.8 up to 15% in different population groups [14, 73–79]. The persistence of the MS in adults is not reported to cause any abnormalities by itself. However, it has been found as a concomitant finding in numerous disorders [16, 80]. Among the causative factors for *metopism* are considered to be stenocrotaphy, plagiocephaly, brachycephaly, encephalic pressure, diminution of muscular pressure, endocrine dysfunction, atavism, heredity and heredo-specific factors [81], an abnormal growth of the cranial bones, hydrocephaly, growth retardation, sexual influence, scaphocephaly and mechanical causes [82].

It has already been established that metopic skulls possess specific distinctive configuration of the neurocranium characterized by a broad forehead with greater inter-frontal and inter-orbital breadths [4, 81, 83–85], as well as a greater frontal curvature [75]. The metopic skulls attain a given capacity by a greater expansion in the forward direction and a smaller development in the hinder part of the vault. Therefore, the *metopism* could not be explained merely by a supposed expansion of the frontal lobes and namely the prefrontal cortex, but rather as an adjustment of the braincase as a whole to its contents [83]. Furthermore, despite the close developmental interrelation between the neuro- and

basicranium, the preservation of the MS along with a specific construction of the neurocranium was not found to be related to an alteration in the cranial base expressed by cranial base angle [86]. All this suggests that the *metopism* is not related to a primary cranial base deformation.

The neurocranial capsule responds secondarily to the primary expansion of the neural mass, consisting of brain, leptomeninges and cerebrospinal fluid, by passive translation of the bones outwards [1]. Hyper- and hypovolumetric growth of the neural mass volume is the primary etiological factor in macro- and microcephaly, respectively. That the volume alone is responsible is well demonstrated by the essentially normal neurocranial sizes and shapes of hydranencephaly [1, 18]. Consequently, the MS persistence is not responsible for the distinctive skull configuration, but rather is an expression of the underlying neural mass specific demands.

5. Metopic suture persistence and frontal sinus development

It has been suggested that the MS preservation suppresses the FS development [27, 40]. A possible explanation has been supposed to be the simultaneous FS development along with the frontal bone growth, most probably with a feedback regulating mechanism. Thus, if the frontal bones fail to fuse, the MS persists and the pneumatization of the frontal sinuses could be retarded or entirely suppressed [32]. Another suggestion is that the MS does not inhibit the FS development itself, but rather the accumulation of both features in nonsyndromic individuals is an expression or an aftereffect of a certain condition during the early development [4]. It is known that the craniosynostosis results in an underdevelopment of the FS due to the increased intracranial pressure (ICP) that hinders pneumatization of the sinuses [87, 88], since the FS development is an inverse ratio to the ICP [89]. However, a surgical enlargement of the neurocranium with an adequate stabilization leads to a decrease in the pressure on the inner frontal cortex; thereafter, the FS pneumatization proceeds normally [88]. Nevertheless, the FS pneumatization seems to depend on the craniosynostosis and on the type of surgery performed [33]. According to McCarthy et al. [87], the fronto-orbital advancement appears to have the detrimental effect on FS development, whereas the strip craniectomy procedures do not. It has been speculated that the path of the ethmoid pneumatization into the FS is interrupted by the saw cut, the gap or defect resulting from the advancement/displacement of the supraorbital bar, as well as residual bone formation. Contrarily, Locher et al. [88] stated that following bilateral fronto-orbital advancement, a nearly regular FS development is possible, with the exception perhaps of the severe cases of Crouzon syndrome. Notwithstanding, if the FS developed after the surgical intervention, it is often located in the roof of the orbits [33].

Besides craniosynostosis, the elevation of the ICP could be a consequence of many other heterogeneous conditions such as haematoma, neoplasm, trauma, seizure, hydrocephalus, meningitis, etc. [90], and most of them are not associated with a distortion of the skull configuration. In newborns and infants, the main signs of acute and chronic elevation of ICP are

suture diastasis (mainly coronal and metopic) and bulging of the anterior fontanelle [90]. The excessive head growth is a major feature for an increased ICP until the age of 3 years since the expansion of the skull volume allows partial venting of the increased pressure [91]. Nonetheless, the normal head growth does not preclude the presence of an increased ICP, as the rate of the pressure increase is also important, because the intracranial structures accommodate remarkably well to slowly increasing pressure, while sudden changes are intolerable and result in definite symptoms [91].

The *metopism* has been supposed to be related with the hypofunction of the thymus inducing a condition of prolonged infantilism, which finds expression in the persistence of the MS. Another suggestion is that the hypopituitarism has been concerned in the MS persistence. Both the hypofunction of thymus and pituitary glands independently result in a retardation of bone growth similar to that in rickets, with a marked deficiency in the normal processes of ossification and a tendency for arrested suture obliteration [81]. The iron deficiency anemia (IDA) is a common type of anemia, which has been reported to be associated with an impaired thymus function [92] and a well-known consequence of hypopituitarism [93]. The IDA has been identified as one of the risk factors for vitamin D deficiency in some populations [94]. Patients with IDA have been reported to feature MS preservation [95]. Furthermore, due to the overgrowing red marrow, the severe IDA causes skull thickening, which in turn involves FS underdevelopment [11, 96]. The IDA has also been associated with an increased ICP [97, 98]. The intracranial hypertension has been supposed to be a possible underlying cause for MS persistence along with the FS underdevelopment [4, 59].

The MS preservations, a delayed closure of the anterior fontanelle and wormian bone formation have been found to be common in patients with Down's syndrome [99]. Underdeveloped FS is also typical of the DS [43]. In patients with DS, the thymus function has been significantly impaired [100]; however, it is still unclear whether or not the short stature in DS involves pituitary hypofunction due to the suboptimal production of the growth hormone, or rather involves hypothalamic dysfunction [101, 102]. Interestingly, the IDA is a frequent condition in DS [103].

It could be seen that the persistent MS along with FS underdevelopment and other common symptoms are typical of heterogeneous disorders like DS and IDA, and both conditions involve or are due to an iron deficiency. The iron deficiency is a widespread nutritional disorder in infants, children and women of reproductive age. It has already been suggested that the *metopism* probably is caused by impairment of the ossification process due to a nutritional deficiency and more exactly the lack of calcium. This suggestion has been based on the assumption that the *metopism* has been more prevalent in the medieval than today, in populations with a low life expectancy and among women who have become pregnant and have given birth immaturely [104]. Bearing in mind the symptoms and consequences of IDA, it seems reasonable to suggest that the MS preservation along with the FS underdevelopment could be an expression or aftereffect of nutritional deficiency and more exactly the iron deficiency during early development. This suggestion could be verified through a purposeful monitoring and longitudinal study of patients with confirmed IDA.

6. Conclusion

The peculiar to the metopic skulls frontal bone configuration is rather an expression of the underlying neural mass demands than a consequence of the MS persistence. Moreover, the persistent MS is frequently associated with FS underdevelopment. It is reasonable to suggest that the MS does not inhibit the frontal sinus pneumatization itself, but rather both traits are expression or aftereffect of a certain condition during the early development.

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Conflict of interest

The authors declare no conflict of interest.

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Section 2

Challenging Issue on Sinus Augmentation

Chapter 2

Management of the Complications of Maxillary Sinus Augmentation

Alper Sindel, Mehmet Mustafa Özarslan and Öznur Özalp

Additional information is available at the end of the chapter

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Abstract

Dental implant rehabilitation of the posterior maxillary region has always been a challenging issue due to both alveolar ridge atrophy and sinus pneumatization. Maxillary sinus augmentation is a well-known and predictable procedure in vertical deficiencies of the posterior maxilla. To date, various techniques have been described based on the physiology of intrasinus bone repair to obtain better outcomes. Nevertheless, these procedures could also be associated with several intra- and postoperative complications such as perforation of the sinus membrane, hemorrhage, infection, graft resorption, and loss of the graft or implants. The aim of this chapter is to review the contemporary methods for maxillary sinus augmentation and to present both recommendations for prevention and management of the associated complications.

Keywords: dental implants, complication, management, sinus augmentation, sinus lift

1. Introduction

Oral rehabilitation with dental implants has been widely practiced with a success rate well over 95% in complete, partial, or single edentulism [1]. However, dental implant placement in the posterior maxillary region is frequently compromised due to certain anatomical and physiological conditions including postextraction alveolar ridge atrophy, pneumatization of the maxillary sinus, and poor quality of residual alveolar bone [2]. Therefore, vertical alveolar ridge augmentation is often mandatory before or in conjunction with the installation of implants [3].

In this regard, maxillary sinus augmentation is a well-known, predictable, and largely required procedure for increasing residual alveolar bone height by elevation of the Schneiderian membrane [4]. Since the introduction of the surgical technique by Tatum [5] in 1976 and Boyne [6] in 1980, various approaches have been extensively studied.

Access to the Schneiderian membrane may generally be achieved directly by lateral approach or indirectly through transcrestal osteotomy. To date, numerous modifications using both approaches have been described, and the vast majority of them have proved their worth and efficacy over the years. Nevertheless, the procedure could also be associated with several intra- and postoperative complications, which may result with a negative impact on the patient's quality of life by additional surgery, hospitalization, and prolonged recovery time. Subsequently, the outcome of the implants and the success of the oral reconstruction procedure may be compromised [4].

Maxillary sinus augmentation procedures are increasingly performed by oral and maxillofacial surgeons, periodontists, dentists, and otorhinolaryngologists worldwide. Prevention and management of the associated complications principally begin with having a thorough knowledge of the sinus augmentation techniques. Thus, the purpose of this chapter is to review the contemporary methods for maxillary sinus augmentation and to present both recommendations for prevention and management of the associated complications.

2. Internal sinus lifting (crestal approach)

The crestal approach involves the elevation of both the Schneiderian membrane and bony floor of the sinus indirectly through the alveolar crest without a preparation on the lateral wall of the sinus. With this technique, the elevation of the sinus floor up to 5 mm without any perforations was shown microscopically [7]. Internal sinus lifting through the transcrestal approach is a well-validated surgical option for situations where there is a minimum of 5–6 mm residual bone height [8]. The technique is considered to be more conservative than the conventional lateral approach and may reduce the operation time and postoperative morbidity [4].

2.1. Surgical technique

Since its introduction in 1986 by Tatum [5], the crestal approach has undergone several modifications in an effort to expand its feasibility and obtain greater success rates with reduced complications [9]. Some of these modifications rely on using medical devices and instruments that are specific to their particular technique. All of these techniques have demonstrated high rates of success; however, there is still insufficient evidence from prospective studies to validate their utility in clinical practice.

2.1.1. Osteotome-mediated sinus floor elevation (OSFE)

OSFE is based on the use of a socket former for the selected implant size for preparing the implant site and hand tapping it in a vertical direction to accomplish a "green-stick fracture" of the sinus floor. Subsequently, implants are placed to support the elevated floor of

the maxillary sinus. In 1994, Summers [8] described a modified approach for OSFE by using a set of conical osteotomes with increasing diameters for both implant site preparation and sinus floor elevation (**Figure 1**). This technique allows to increase the bone density, resulting in better primary stability of inserted dental implants.

2.1.2. Bone added osteotome-mediated sinus floor elevation (BAOSFE)

BAOSFE, also referred to as the "Summers technique," is a combination of the OSFE technique with the addition of a bone graft material. The mass of the native bone and the graft material is utilized as a hydraulic plug by the upward push of the osteotome to elevate the sinus floor. Subsequent placement of the implants facilitates the elevation of the sinus membrane by tenting it with their apical end. Various graft materials may be used such as autogenous bone, allografts, xenografts, and alloplastic bone materials [10]. There have been a number of studies claiming the necessity of bone graft material to keep the volume of the sinus membrane [11], whereas others have reported favorable results and reduced risk of infections without the use of any bone graft [12].

2.1.3. Minimally invasive antral membrane balloon elevation (MIAMBE)

MIAMBE is a modification of the BAOSFE method in which sinus lift is performed by the insertion of a specially designed balloon through the osteotomy site on the alveolar crest, insufflating it with saline solution through a catheter in order to detach the sinus membrane. This technique is intended to be applied to alveolar crests measuring 3 mm or less and provide a gain in height up to 10 mm with few intraoperative complications [13].

2.1.4. Hydrostatic sinus lift

Hydrostatic sinus lift technique, first proposed by Chen et al. [14] in 2005, relies on the principle of lifting the Schneiderian membrane using hydraulic pressure. Following the initial drilling, the drill is connected to a pump that produces high hydraulic pressure, which is used to break the sinus floor and to lift the membrane. Along with the recent developments, this technique is supposed to provide reduced risk for sinus membrane perforation, minimal trauma, and postoperative complications for sinus lifting surgery [15].

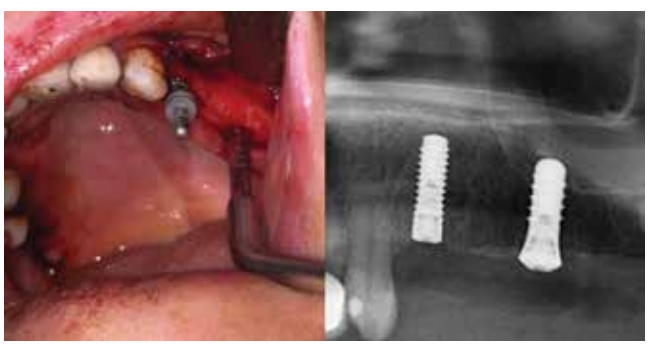

Figure 1. Use of conical osteotomes for both implant site preparation and sinus floor elevation and simultaneous implant installation.

2.2. Internal sinus lift complications: Prevention and management

Internal sinus lifting is associated with several intraoperative and postoperative complications, which may compromise the outcomes of the treatment and health of the patient. An in-depth overview on causes, prevention, and management of these complications is presented later.

2.2.1. Intraoperative complications

2.2.1.1. The Schneiderian membrane perforation

The main drawback of this procedure is the uncertainty of a possible perforation of the Schneiderian membrane because the sinus lifting procedure is performed blindly due to the impossibility to visualize the sinus floor [5, 6]. The incidence of membrane perforations in osteotome-mediated sinus lift has been reported to range between 4 and 25% [16], while such complication has been described in 25–44% of external sinus lifting cases [17]. It should also be noted that microlacerations are impossible to detect in many cases; thus, the true incidence may be higher than currently reported. Perforation of the sinus membrane may lead to the development of sinusitis, epistaxis, exfoliation of graft particles from the nose, or a patent oral-antral communication. Development of a sinus tear during the internal lifting may not always be determined with the Valsalva maneuver or more accurately by the inspection with an endoscope [18].

Membrane perforation may occur due to several factors related with anatomy, excessive tapping, or overzealous elevation. One possible anatomical challenge may be an oblique sinus floor at the site of preparation, which may lead difficulty in initial in-fracturing and resultant membrane perforation. Likewise, thin sinus mucosa and irregularities of the bony sinus floor such as sharp ridges, antral septa, and spines may pose risks for membrane perforation [19]. Furthermore, elevation of the Schneiderian membrane beyond its capacity may also cause the membrane to tear. To date, a wide range between 2 and 10 mm has been reported for height of sinus elevation using transcrestal techniques [2, 7, 13, 18]. A thorough clinical and radiological examination should be carried out to evaluate the anatomy of the sinus, the presence of sinus pathology, and the residual alveolar bone height. Additionally, intraoperative use of sinuscopy has been suggested to allow for elimination of any sinus pathologies, control of the graft position, and reduction of the risk of sinus membrane perforation and postoperative complications [7].

Although it has been reported that a gain up to 10 mm in alveolar height can be achieved using several modifications of transcrestal approach, it has commonly been assumed that the Schneiderian membrane can be safely elevated for 5 mm through the internal sinus lifting [7, 20]. Therefore, it should be kept in mind that the maximum elevation height obtainable with transcrestal techniques differs interindividually because it highly correlates to the elastic properties of the Schneiderian membrane and the maxillary sinus anatomy as well as the surgical technique of force transmission [21]. The osteotomes should not be tapped or advanced beyond the sinus border. Further attempts for the prevention of membrane perforation may include inserting a collagen membrane into the osteotomy and not to use the particulate graft materials with sharp nature.

Unfortunately, when membrane perforation is detected during the procedure, there is no possibility to repair the torn membrane without changing to a lateral surgical approach because

of the limited access [18]. A number of researchers have reported that small perforations show complete recovery in 6 months spontaneously, and it is not required to abort the simultaneous placement of implants or bone grafts [18, 19]. However, if high risk of infection is suspected or the size of perforation is large, postponing the surgery or repairing the perforation through a lateral approach should be considered.

2.2.1.2. Inadequate primary stability

Implant stability initially relies on the host bone present at the created osteotomy site, while future additional support is potentially gained by the consolidation and amalgamation of the grafted material with newly formed host bone. Optimal primary stabilization at the time of implant placement is essential for implant success and survival [22]. Lack of primary stabilization may be related to insufficient bone height/width, poor bone quality, or overtreatment with the osteotomes. In cases where poor bone quality is encountered, consideration might be given to greater use of the osteotome versus drilling to increase the bone density and implant stability [22]. Further attempt might include the underpreparation of implant bed with either osteotomes or drills and insert a substantially larger diameter implant to maximize the primary stability. However, it should also be kept in mind that underpreparation may lead to excessive compression during the implant installation and resultant fracture of the bony trabeculae and poor recovery of vital bone. By the same token, the use of tapered implants versus parallel-walled implants has been shown to increase the primary stability in low-density bone as they have higher insertion torque during the placement [23]. Moreover, rough-surface implants are also recommended because they are more prone to adhesion of the bone fragment surfaces resulting in an increased bone formation [24].

2.2.1.3. Displacement of the implant to the sinus cavity

Although reportedly uncommon, accidental displacement of the implant into the sinus cavity may occur due to poor bone quality, untreated membrane perforation, and the use of excessive force during the installation [25]. The prevalence is probably underestimated due to the lack of cohort studies and few case reports that have been published [26]. A displaced implant should be removed from maxillary sinus as soon as possible to avoid further complications such as maxillary sinusitis, narrowing of the ostium, or reduced ciliary movements, impaired mucociliary clearance, pseudocyst formation, aspergillosis, migration into the ethmoid sinus, orbital floor, sphenoid sinus, or even the cranial fossa, orbital cellulitis and optic nerve damage, meningitis, or brain abscess [27–31]. Different techniques have been proposed for the removal of a displaced implant from the sinus using a transnasal or transoral approach [32]. The use of transnasal endoscopy has the advantages of a low morbidity, rapid recovery, and treatment of paranasal sinusitis, which, however, has several limitations including the requirement of a specific equipment, specialized surgery rooms, and often general anesthesia [33]. Moreover, the location and size of the implant have to pass through the ostium [25]. Alternatively, a transoral approach with the creation of a bony window in the anterior-lateral wall of the maxillary sinus can be performed. Transoral surgical techniques may remove implants successfully allowing a better visibility combined with the ability to remove even large implants under local anesthesia [32]. On the other hand, since this approach diminishes the integrity of the lateral wall of the maxilla, the access window may not completely reossify [34].

2.2.2. Postoperative complications

Postoperative infection, implant loss, benign paroxysmal positional vertigo, hemorrhage, nasal bleeding, blocked nose, hematomas, and loosening of cover screws are among the reported complications following the OSFE procedure.

2.2.2.1. Infection

Site infection is not only the most common postoperative complication but also among the foremost etiologies of possible complications. Infection may occur due to poor oral hygiene, contamination of the implant surface or graft material, and underlying diseases of the sinus. Particular attention should be paid to minimize the bacterial load during the surgery. The site should be evaluated for the presence of any active periodontal disease or endodontic infection. Moreover, the use of preoperative and postoperative antibiotics and antiseptic mouth rinses is also recommended to decrease potential pathogenic bacteria [35].

2.2.2.2. Benign paroxysmal positional vertigo (BPPV)

BPPV is a common vestibular end organ disorder characterized by short, repeated, brief periods of vertigo that are triggered by certain head movements in the plane of the posterior semicircular canals [36]. Recent evidence suggests that BPPV may occur as an early postoperative complication following OSFE [37]. It has been reported that the percussive forces of the surgical mallet may lead to the detachment of the otoliths from the otoconia layer of the utricular macula and cause them to float around in the endolymph [36, 38]. Moreover, hyperextension of the head during the operation favors the displacement of these free-floating particles into the posterior semicircular canal, creating the position- or motion-induced vertigo [39].

The diagnosis of BPPV is commonly established by the Dix-Hallpike test [40]. The patient experiences vertigo and a characteristic torsional nystagmus when moved quickly into a supine position with the head turned, so that the affected ear is 45° below the horizontal plane [41]. The direction of nystagmus is essential to specify the affected canal as both the vertical and the horizontal semicircular canals may be affected. The posterior canal is by far the most frequently affected canal (80–90%); involvement of the horizontal (lateral) canal is accounting for 5–30%, and the anterior canal is 1–2% of patients [42–44].

The treatment modalities of BPPV include follow-up of the patient, vestibulosuppressant medication, vestibular rehabilitation, repositioning maneuvers, and surgery [45]. Recent evidence supports that the repositioning maneuvers may effectively help in eliminating the vertigo due to BPPV, reducing the risks of falling, and improving the quality of life [44]. To date, several methods with different sequential head movements have been proposed to move otoconial debris from the semicircular canal to the utricle. Among these, the Epley maneuver (canalith repositioning procedure, CRP) and the Semont maneuver (the liberatory maneuver) have been proposed for the treatment of posterior-canal-type BPPV, while the lateral-canal-type BPPV is usually treated with the Lempert maneuver [46–48]. In addition, self-treatment exercises such as the Brandt-Daroff exercise have also been recommended for treatment of any types of BPPV [42, 49].

The incidence of OSFE-induced BPPV has been reported to be less than 3%, and the condition is self-limiting as symptoms subside or disappear within 6 months of onset [39]. However, the symptoms involved may be sufficiently severe to significantly alter the patient's daily life [41]. It is important to be aware of and inform patient about BPPV when performing OSFE. To prevent this complication, gentle hammering with a safe head position should be taken during the procedure. In suspected cases of BPPV, immediate referral to an otorhinolaryngologist is highly recommended.

2.2.2.3. Implant loss

Despite the high success rate, implant failures may occur as a consequence of abovementioned complications and patient-related local and systemic factors [50]. It has been reported that implant failures associated with OSFE usually occur before loading [51]. A subantral bone measured 4 mm or less at the time of implant placement has been shown to be associated with an almost 10–20% increase in implant failures [52]. Osteotome technique is usually recommended when more than 6 mm of residual bone height is present, and an increase of about 3–4 mm is expected.

3. External sinus lifting (lateral window technique)

Maxillary sinus floor augmentation using the lateral window technique was originally described by Tatum [5] in 1977 and subsequently published by Boyne [6] in 1980. This technique is still the most frequently used method to increase the amount of bone in the posterior maxilla before or in conjunction with implant placement [53].

3.1. Surgical technique

The technique is mainly based on the sequential steps of a trapdoor osteotomy on the lateral wall of the maxillary sinus and elevation of the Schneiderian membrane to create a confined space for the placement of graft material and dental implant. Over the past 30 years, lateral window technique has undergone numerous modifications including different techniques, graft materials, and implant placement protocols to increase the predictability of the procedure and reduce the rate of complications [53].

3.1.1. Antrostomy techniques

An antrostomy is made in the lateral sinus wall to get through to the Schneiderian membrane in order to create a space for the placement of the bone graft material and the implant. The size of the window should be wide enough to achieve sufficient access and vision to perform the membrane elevation and graft placement without complications. On the other hand, redundant expansion of the window should be avoided because it would compromise the blood supply to the graft.

Osteotomy can be made with either the rotary technique or the piezoelectric technique. The rotary technique is performed using a high-speed handpiece or surgical motor and

preferably a round diamond or carbide bur. In line with the recent trend toward minimally invasive surgery, the use of piezosurgery has been reported to eliminate the "drag" created by rotary instrumentation and be less associated with the damage to the blood vessels or the Schneiderian membrane [54]. Furthermore, different approaches have also been described regarding the creation technique of the window. One method of creating the access window is abrading away all of the bone in the window area with a lateral cutting motion. As the bone is thinned, the sinus membrane is visualized as a blue shadow, and the thin bony layer is gently removed, creating a complete osteotomy (**Figure 2**). Another method is performing a trapdoor osteotomy in which the superior osteotomy cut is kept partially incomplete, and the lateral wall "window" is rotated (hinged) inward and upward to a horizontal position (**Figure 3**). Alternatively, a complete osteotomy can be performed extending 360° to create a bony island in the center. This can remain pedicled to the membrane and being elevated with it, or it can be removed to be used later for recovering the window (**Figure 4**). In reviewing the literature, there is no evidence that one approach is more favorable than another.

3.1.2. Bone grafting materials

A considerable amount of literature has been published on different types of biomaterials including autograft, allograft, xenograft, alloplast, and growth factors; however, debate continues about the ideal graft material for the maxillary sinus floor augmentation [55].

Figure 2. Access to the sinus through the abrasion of the bone and graft placement.

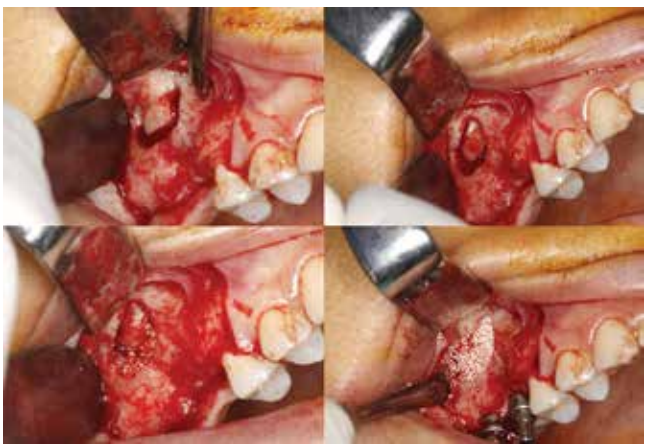

Figure 3. Access to the sinus performing a trapdoor osteotomy and simultaneous implant placement.

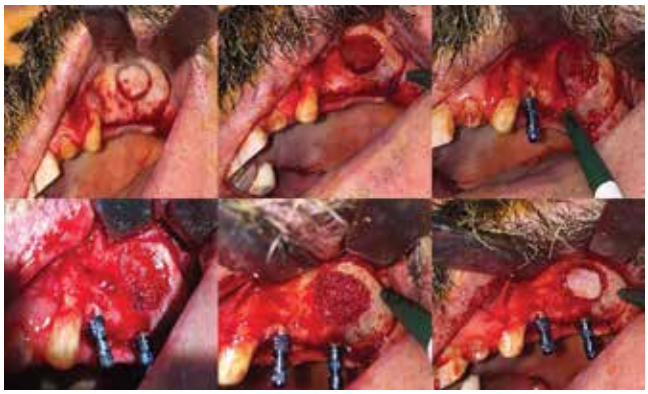

Figure 4. Access to the sinus by creation of a bony island and simultaneous implant placement. The bony island is used to re-cover the window.

Although autogenous bone graft has always been considered the gold standard in augmentation procedures due to its osteoinductive, osteogenic, and osteoconductive characteristics, the procedure is also associated with increased morbidity and significant graft resorption [56]. Therefore, the use of various bone replacement grafts of biologic or synthetic origin has become a major area of interest in order to simplify the surgical procedure by eliminating the need for bone harvesting [57]. Recent evidence suggests that implant survival rates with bone replacement grafts, particularly xenografts as the most rigorously evaluated substitute, are equal to or better than that achieved with autogenous bone [55].

On the other hand, there has also been an alternative concept of lateral window technique, which relies on using the implant to tent the membrane without a bone graft material [58]. Subsequent to the elevation of the Schneiderian membrane similar to the surgical protocol described above, simultaneous implant placement is performed. The blood clot formed around the exposed implant tip or a centrifuged autogenous blood product is used as the sole grafting material. Although several studies have demonstrated favorable results with high survival rates, there is still a lack of long-term clinical and radiographic studies on the amount of bone formation and final treatment outcome with this surgical intervention [58]. Thus, further research is needed to validate the outcomes and predictability of maxillary sinus lift applying the lateral window technique without a graft material and simultaneous implant installation.

3.1.3. Timing of implant placement

A one- or two-stage implant placement approach has been suggested in conjunction with lateral window maxillary sinus lift procedures. In two-stage technique, following the sinus augmentation and a healing period of 6 months or more, implants are placed with a second surgical intervention. Therefore, the one-stage procedure has been proposed in order to shorten the total period of treatment and to eliminate the requirement of a second surgery, thus reducing morbidity and cost [59]. Traditionally, a minimum of 4–5 mm of residual bone height is recommended for simultaneous implant placement with direct sinus lift to ensure initial stability [60]. On the other hand, recent clinical evidence also suggests that the simultaneous placement of implants with direct sinus lift may be a feasible treatment modality as

long as adequate primary stability can be ensured, regardless of the recommended minimum residual bone height [61].

3.2. External sinus lift complications: Prevention and management

Although complication rate associated with the direct sinus lift procedure in the literature is quite low, several potential complications have been reported that increase the morbidity and jeopardize the treatment outcome [62].

3.2.1. Intraoperative complications

Surgical difficulties encountered during the course of the procedure may lead to the occurrence of several intraoperative complications. These difficulties may arise from the presence of complex anatomic situations, the choice of less predictable treatment options, inadequate systemic or local diagnosis, or operator error. The most frequent intraoperative complications are the Schneiderian membrane perforation and bleeding, while the others include the obstruction of the antral meatal ostium complex, dislocation of the implant into the sinus cavity, perforations in the buccal flap, and less frequently, injury to the infraorbital nerve [17, 63].

3.2.1.1. The Schneiderian membrane perforation

Sinus membrane perforation, being the most common complication during the sinus lift surgery, has been reported to occur with a range of incidence comprised between 20 and 44% of cases [17]. Membrane perforation may be encountered during different phases of the procedure including preparing the antrostomy, removal or turning over the bony window, raising the membrane, and placing the graft. Moreover, thin membrane, the presence of Underwood's septa, thick or convex lateral walls, a sharp angle between the buccal and palatal walls of the antral cavity, especially when below 30°, irregularities of the sinus floor due to the protrusion of the root profiles, previous interventions of the sinus, and a decreased residual alveolar height less than 3.5 mm are among the anatomical risk factors that prompt the occurrence of membrane perforation [64].

A precise evaluation using computed tomography (CT) may aid to determine the 3D anatomy of the sinus to minimize the rate of perforation. When septa are known to be present, lengthening the window in the anteroposterior direction is recommended in order to allow for a lateral-to-medial elevation of the membrane from both sides of the septum. An alternative to this approach is the creation of two separate windows; however, one should consider that this technique may result in small windows, which can complicate the access and vision [65]. Use of piezoelectric surgery has been proposed to be a valuable adjunct to sinus surgery, which has been shown to result in decreased membrane perforation rates [54]. Other considerations to prevent membrane perforation include using diamond burs and elevation of the membrane from lateral to medial while keeping the instrument in contact with the bone at all times.

Nevertheless, perforation is unavoidable in some cases despite accurate presurgical radiographic evaluation and ideal surgical maneuvers. Perforation of the sinus membrane may result in bacterial contamination and infection of the graft and dispersion of the particulate, leading to impairment of the functional homeostasis of the antral cavity [60]. Once the

perforation is confirmed, the exact size of the perforation should be detected by gently raising the surrounding membrane to reduce the tension and to avoid further tearing. Minor perforations of less than 1 mm may self-repair by membrane foldover or clot formation, thus permitting simultaneous implant placement. In perforations smaller than 5 mm, using fibrin glues, collagen tapes, and bioabsorbable membranes or suturing the membrane is usually sufficient for closure that allows simultaneous implant placement. Membrane perforations larger than 5 mm may require bioabsorbable membranes, lamellar bone plates, suturing either alone or in combination with fibrin glue, or abandoning the intervention. Regardless of the size and repair method of the sinus membrane perforation, there should be no doubt about the stability of the perforated area to contain the graft material.

Since large perforations constitute an enormous challenge, several authors have studied and suggested specific repair methods based on the use of collagen membranes, local flaps, and autogenous bone blocks. Among these methods, "the Loma Linda pouch technique," which was introduced by Proussaefs et al. [66] in 2003, involves covering all internal bony walls of the sinus using a slow resorbing collagen membrane simulating the natural membrane and folding the membrane on the lateral wall with external tack fixation. However, pouch formation surrounding the graft material can impair the blood supply coming from the walls of the sinus, thus representing an impediment for the maturation of the graft and the recovery period [67]. More recently, "the intrasinusal locking technique" has been proposed by Sindel et al. [68], which allows for simultaneous implant placement in the presence of a large membrane perforation aiming to decrease the number of surgical interventions and the complications related to surgery. In this technique, autogenous bone ring blocks harvested from mandibular symphysis are placed internal to the floor of the maxillary sinus and stabilized with the simultaneously installed dental implant, using a mechanism similar to that of a screw and nut (**Figure 5**). The authors reported an implant survival rate of 90% without any postoperative complications such as maxillary sinusitis or infection.

3.2.1.2. Excessive bleeding

Intraoperative bleeding is the second most common intraoperative complication of sinus lift procedure [63]. Massive bleeding frequently occurs from damage to the alveolar antral artery (AAA), which is an intraosseous anastomosis between the posterior superior alveolar artery (PSAA) and the infraorbital artery. There is also a possibility of bleeding from extraosseous anastomosis of PSAA and infraorbital artery during the flap elevation and from posterior lateral nasal artery [69].

Although being usually minor, in some cases, bleeding may be difficult to control in a timely manner and induce additional complications such as membrane perforation, impairment of blood supply, and displacement of the graft material [63]. Preoperative evaluation using cone beam–computed tomography (CBCT) may help to create a window respecting the integrity of vascular structures [70]. Further attempts to decrease the risk of bleeding may include preparing the window through the piezosurgery or preferring the diamond burs than carbide burs when rotary instrumentation is used [54]. Management of vascular bleeding during the sinus lift procedure can be carried out by raising the head, applying the direct and firm pressure on the bleeding point, crushing the bone around the vessel, using local vasoconstrictor agents

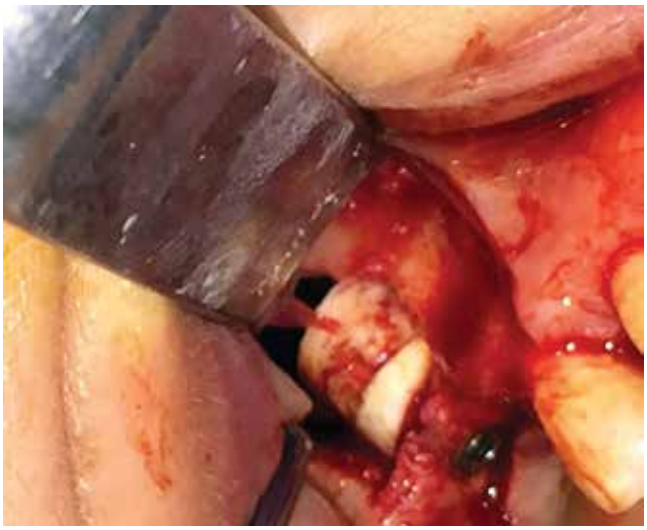

Figure 5. "Intrasinusal locking technique": Autogenous bone ring inside the sinus cavity is locked to the alveolar crest through the dental implant.

or bone wax, and suturing the vessels [17]. In addition, bleeding can be controlled through the use of electrocautery; however, much attention should be paid not to cause membrane perforation [71].

3.2.1.3. Other complications

Improper surgical technique may lead to the tears in the buccal flap while trying to achieve a tension-free closure. Hence, redundant release of the buccal flap should be avoided respecting to the thickness of the flap and convexity of the malar eminence. Likewise, advanced closure methods such as pedicled buccal mucosal flap should be considered in cases where sufficient tension-free closure could not be achieved by buccal flap release. Yet, another complication related to poor surgical technique is the infraorbital nerve damage, which may result from pressure during the flap retraction or dissection for releasing the flap for closure [72]. Care should be taken to identify and protect the nerve while performing surgery near the infraorbital nerve. Additionally, overfilling of the graft material should be avoided because it may lead to the obstruction of the antral meatal ostium complex [63].

3.2.2. Postoperative complications

Infection of the graft, acute sinusitis, flap dehiscence, over-filling necrosis, loss of graft material, formation of oroantral fistula, migration of dental implants into the sinus cavity, implant failure, cyst formation, and BPPV are among the postoperative complications specific to external sinus lift procedure. Furthermore, a number of nonspecific patient responses may also be encountered including edema, hematoma, minor nosebleed, and mild congestion likewise any other surgical procedure.

3.2.2.1. Graft infection

Sinus graft infection is a rare but important complication with a reported incidence up to 4.7% [73]. Various factors have been reported to predispose the graft infection such as preexisting sinus infection, membrane perforation, contamination of the graft with saliva, wound dehiscence, and inadequate aseptic technique. The symptoms of the graft infection include tenderness, fistulation, suppuration, severe pain, facial swelling, abscess, elevated body temperature, and loss of graft particles through the fistulous tracts (popcorn sign).

The condition needs to be urgently treated due to the risk of quick spread of the infection to the adjacent structures, which may result in infraorbital abscess, orbital cellulites, and even brain abscess [74]. Several modalities involving irrigation, drainage, administration of systemic antibiotics, and partial or total removal of the graft material have been proposed for the treatment [75]. Superficial infections may be treated with the use of antibiotics alone; however, this modality may result in further progression of the infection requiring the complete removal of the graft. Recently, Mahler et al. [76] have described "the Dome phenomenon," which refers to a dense, solid, hard tissue maintained in the superiormost aspect of the grafted area in case of a graft infection. They reported successful outcomes with partial removal of the infected graft until this dome-shaped area indicating the regenerative potential of the Schneiderian membrane. Generally, the use of a new augmentation material is not recommended to prevent repeated infection because the thorough elimination of infected graft material can enable spontaneous bone fill in majority of the cases.

3.2.2.2. Acute maxillary sinusitis

The altered anatomic relation of the antral floor along with a hematoma or a seroma that fills up the maxillary sinus may lead to the obliteration of the osteomeatal unit [77]. Furthermore, the displacement of the graft materials through the sinus membrane or overfilling of the sinus may also result in the impairment of mucociliary clearance. Apart from these, aberrant anatomical factors such as ostium stenosis or preexisting sinus disease may also facilitate the development of acute sinusitis following the sinus lifting procedure [78]. Acute maxillary sinusitis may jeopardize the survival of the implants and the graft. Medical treatment with decongestants and antibiotics should be obtained in patients with a predisposition to sinusitis. In addition, consultation with an otolaryngologist should be considered to confirm whether the management of sinusitis can be carried out conservatively or the sinus patency requires additional surgical intervention.

3.2.2.3. Other complications

Increased intrasinus pressure may result in overflow of the graft material through the window and consequent wound dehiscence in the early postoperative period. This rare complication may be avoided by placing and stabilizing a membrane over the window or recovering it with the intact bony window.

As well as being an intraoperative complication, the dental implant migration into the maxillary sinus may also occur after several months or even years of its adequate functioning [79].

Various factors have been suggested to explain the mechanism of late migration including the changes in intrasinusal and nasal pressures, the lack of osseointegration, peri-implant bone destruction due to an autoimmune reaction, and the resorption produced by an incorrect distribution of occlusal force [80]. (See Section 2.2.1 for the management.)

Another unusual complication of direct sinus lift procedure is the formation of an oroantral fistula, which results from the progressive sinus infection and ostium blockage [81]. Following the elimination of the sinus infection, different techniques such as buccal flap, palatal rotation-advancement flap, and buccal fat pad can be used for the treatment of the oroantral communication.

4. Conclusion

Maxillary sinus augmentation, either crestal or lateral window approach, is a well-known, predictable, and often mandatory procedure to increase the alveolar bone height in posterior maxilla for dental implant rehabilitation. However, the procedure is also associated with certain complications that may influence the outcome of the therapy and patients' quality of life. A thorough knowledge of prevention and proper management of these complications is essential to obtain better treatment outcomes.

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Chapter 3

Sinus Lifting and Leucocyte- and Platelet-Rich Fibrin

Berkem Atalay

Additional information is available at the end of the chapter

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Abstract

The insufficient alveolar bone height due to the maxillary sinus in the posterior maxilla and postextraction bone resorption may limit implant placement. The sinus lifting procedure creates space between the maxillary alveolar bone and the Schneiderian membrane, which is filled with graft materials to maintain adequate space for new bone formation. Leucocyte- and platelet-rich fibrin (L-PRF)-mixed bone substitute or L-PRF has been used solely as a graft material for sinus lifting. The clinical and radiological findings of the application of PRF for sinus augmentation have been shown to have good results regarding new bone formation. The L-PRF can be an efficient biomaterial for graft particles in maxillary sinus lifting.

Keywords: sinus lifting, leucocyte- and platelet-rich fibrin, bone graft, L-PRF block, Schneiderian membrane

1. Introduction

Alveolar bone resorption in the edentulous ridge can cause insufficient bone volume for placing dental implants and consequently cannot be rehabilitated by prosthetics. Sinus lifting is a surgical approach with the elevation of the Schneiderian membrane to place the bone grafts for treatment of atrophic posterior maxilla [1]. This surgical technique is a successful treatment for augmentation of the atrophic posterior maxilla and to gain bone volume for dental implant procedure [2].

Sinus lifting shows complexity due to anatomical variations and Schneiderian membrane. The lateral bone's thickness changes the risk of membrane perforation. Evaluation of the thickness of the lateral wall before surgical treatment may affect the integrity of the Schneiderian membrane during the surgery [3].

Sinus lifting is a predictable technique, but various complications can occur during surgery or postoperative period [3]. These complications can be listed as edema, perforation of Schneiderian membrane, sinusitis development, bleeding, wound dehiscence, postoperative wound and bone graft material infection, implant failure if it is placed simultaneously, and disruption of normal sinus physiologic function. These complications can delay the healing process and may require additional surgeries [4–6]. Cone-beam computed tomography (CBCT) provides an accurate evaluation of the sinus and related anatomical structures. Danesh-Sani et al. recommend using CBCT before surgery to minimize the risk of Schneiderian membrane perforation [7].

Presurgical evaluation with CBCT has become an essential tool for diagnosis and surgical planning, including sinus lifting. Before performing a sinus lift, the clinician's attention should not be only directed to the patency of the ostium through CBCT, because many anatomical features could influence the surgical approach of sinus lifting.

Postoperative swelling of the Schneiderian membrane mostly occurs with maxillary sinus lifting procedure. The mucosa of the Schneiderian membrane heals rapidly and recovers its homeostasis. If the ostiomeatal complex is unfavorable due to anatomic variations, its healing can be delayed, and risk of sinusitis is increased. The ostiomeatal complex plays an essential role in the development of maxillary sinusitis by dysfunction of the mucociliary system. If the patency of the ostiomeatal complex is interrupted, clearance of the maxillary sinus can be delayed and can increase the risk for development of sinusitis [8].

Surgeons must consider the risk of infectious sequelae after sinus lifting. The inflammatory reaction after any surgical procedure is unavoidable. Because of the interference of ciliary activity caused by the elevation of the Schneiderian membrane, altered mucous composition and bacterial infection can occur [9]. After sinus lifting, the maxillary sinus may be filled with hematoma or seroma. However, a mild inflammatory reaction can occur as a regular physiological activity of the nasal airway, and swelling of the mucosa can cause obstruction of the patency of the ostiomeatal complex. As a result, sinus lifting might compound the physiological drainage of the maxillary sinus into the middle meatus by inflammatory swelling on the mucosa of the ostium can predispose the patient to acute maxillary sinusitis [10]. Persisting effect on the ciliated mucosa can be expected because of raising the mucosa of the maxillary sinus [11]. The maxillary sinus mucosa can adapt adequately to the alteration following sinus lifting [12]. It is generally assumed that altered maxillary sinus, such as elevation of the Schneiderian membrane with curving outward or injured sinus mucosa, might change the physiological activity of the maxillary sinus.

Anatomic variations of the maxillary sinus are commonly detected, with an estimated prevalence of 68% [13]. Some anatomic variations on the lateral nasal wall, such as the deviated nasal septum, concha bullosa or paradoxical middle turbinate, and bending of the uncinate process are significant because of their help to the blockage of ostiomeatal complexes. These variants can interfere with drainage and ventilation of the maxillary sinus, and can affect the risk of sinusitis [14]. Compromised maxillary sinus drainage is closely associated with a reduction of the maxillary ostium. Reduced size of the ostium diameter can cause sinusitis [15].

The risk of Schneiderian membrane perforation during sinus lifting, in the presence of antral septa, can be increased [1]. Antral septa divide the sinus into compartments and smaller

accessory sinuses [16, 17]. The presence of septa may constitute a risk factor by causing the Schneiderian membrane to become perforated during surgery. The development of sinusitis is one of the possible complications associated with perforation of the Schneiderian membrane [9]. For the repair of such perforations, there are a variety of techniques, including a buccal fat flap, fibro-mucosal grafts, connective tissue, resorbable collagen membranes, amnion-chorion barriers, and the leucocyte- and platelet-rich fibrin (L-PRF) [18]. Obtaining L-PRF consists of a very simple and inexpensive protocol that produces a strong membrane after compression [19].

L-PRF acts as a bioactive bridge and releases growth factors. The release increases day by day and reaches its highest level on the 14th day and continues until the 28th day [20–22]. L-PRF has certain effects on wound healing [19]. The leukocytes and cytokines have a significant role in controlling infectious and inflammatory processes. While the fibrin matrix is resorbed, cytokines are released to accelerate neovascularization and protect from infection. So, when L-PRF is used in membrane form, it stabilizes the graft material, covers the perforation since it has an inherent attachment to the Schneiderian membrane [23], and protects the wound [18, 24] (https://youtu.be/vuHPSpBVCl8).

The limited quantity of autogenous bone graft in sinus lifting with high morbidity rates is important for the clinicians using bone substitutes rather than the autogenous grafts. So, the investigation of optimal biomaterial combinations to enhance bone regeneration properties is in progress [25, 26]. L-PRF with bone graft for sinus lifting is accelerating bone regeneration. Choukroun et al. reported that healing time between sinus lifting and implant placement could be reduced by using L-PRF [27].

The use of L-PRF with a high concentration of platelets, growth factors, and leucocytes may increase the development of new bone. The liquid L-PRF (i-PRF) has been proposed to agglutinate the bone substitute [28]. Mixing i-PRF with bone substitute creates the L-PRF block.

2. L-PRF block

Prior to sinus lifting surgery, 8–16 tubes of venous blood needed to be collected from the patients. Two tubes should be separated as a white cap, plastic coating, and placed in the centrifuge at 2700 rpm for 3 minutes. The remaining tubes as a red cap, glass coating should be placed in the centrifuge at 2700 rpm for 12 minutes.

The liquid fibrinogen in the white cap tubes has to be aspirated with a sterile syringe. When the centrifugation of the red cap tubes finishes, the L-PRF clots can be removed from the tubes and compressed using a sterile metal box to mold membranes (**Figure 1**).

For the preparation of the L-PRF block as described by Cortellini et al., L-PRF membranes are cut and mixed with a bone substitute at a ratio of two membranes with 0.5 g bone substitute. The liquid fibrinogen needed to be added to the homogenous mix and stirred for at least 10 seconds for the ideal form. By the chopped membranes, fibrinogen is polymerizing into platelets and leucocyte, forming the L-PRF block (**Figure 2**).

Figure 1. The ready-to-use L-PRF membranes in preparation kit.

Figure 2. The L-PRF block.

3. Conclusion

The L-PRF block is secreting bioactive molecules like; a platelet-derived growth factor, bone morphogenetic proteins, insulin-like growth factor, vascular endothelial growth factor, transforming growth factor-β1, and transforming growth factor-β2 [29].

L-PRF can have a positive effect on bone regeneration and osseointegration. Easy preparation of L-PRF, biological properties, and low cost could be considered as reliable support in sinus lifting surgery. The use of sufficient L-PRF clots and membranes, avoiding to close the patency of ostium, is crucial to gain a covetable bone volume [30] (**Figure 3**).

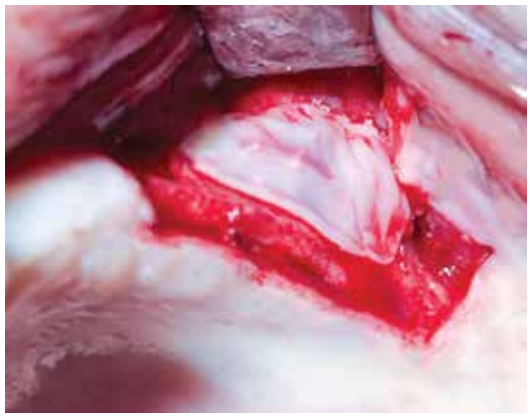

Figure 3. The use of the L-PRF membrane to cover the lateral window.

The L-PRF block maintains the volumetric stability of the biomaterial during healing and by this way, it can prevent the shrinkage of the scaffold. The effects of L-PRF on tissue healing by the release of growth factors and increasing angiogenesis and osteogenesis can lead to the higher volume of newly formed bone with the L-PRF block [31]. The L-PRF block can be a successful new procedure for sinus lifting after further investigations with histological analysis and randomized controlled clinical trials.

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Section 3

Challenging Issue on Rhinosinusitis and Sinonasal Neoplasms

Chapter 4

Medical Management of the Paranasal Sinus Infections

Mehmet Şentürk

Additional information is available at the end of the chapter

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Abstract

Rhinosinusitis is a common disease among all the sinus diseases, and unsuccessful attempts to these infections may result not only in economic burdens but also in increasing the numbers of untreated patients in the community. Medical management of the rhinosinusitis includes antibiotics, antihistamines, nasal decongestants, corticosteroids, mucolytics, leukotriene antagonists, and nasal irrigations. Each treatment option must be selected for appropriate patient and prescriptions must be tailored according to the patient's need. These needs must depend on the endoscopic examination, symptoms, and sinus cultures and computed tomography. It is also a matter of debate whether these investigations lead to treatment or not, but it would be wrong to expect that a single examination method and physical examination alone should direct treatment in the first place. As a result, managing the process with the most appropriate examination methods for the patient's complaints will be the most beneficial approach.

Keywords: acute rhinosinusitis, chronic rhinosinusitis, pediatric, adult, nasal polyp, antibiotic

1. Introduction

Rhinosinusitis is the major public health problem among the upper respiratory tract infections that produce enormous consequences that source the negative effect on the quality of life of the patient and cause significant morbidity and mortality. Rhinosinusitis also has a significant effect on the health economics. In the United States, the predicted yearly amount of the burden has been estimated at $3.5–5.8 billion, especially $1.8 billion for first 12 years of age [1]. It seems that rhinosinusitis affect the quality of life of the children and cause economic loss. It is imperative to obtain up-to-date and accurate information for each physician who is involved in the treatment of this disease group and related ones. In this chapter, updated

information has been given about the medical treatments on pediatric acute rhinosinusitis, pediatric chronic sinusitis, adult acute rhinosinusitis, adult chronic rhinosinusitis without nasal polyp (CRSsNP), and adult chronic rhinosinusitis with nasal polyp (CRSwNP). This information has been compiled from very important guidelines and articles by authors. In this way, the reader will be able to acquire much more detailed and accurate information as well as the source of the information to be obtained.

2. Medical management of pediatric acute rhinosinusitis

2.1. Oral antibiotics

Oral antibiotic treatment is not necessitating the majority of the acute rhinosinusitis (ARS) patients. Viral infections that resolve without therapy are the main cause of rhinosinusitis [2]. A minor proportion of these patients develop a subsequent bacterial inflammation that will heal with antimicrobial treatment. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, Group A beta-hemolytic *streptococci,* and *Staphylococcus aureus* are the most common cause of the development of rhinosinusitis. Therefore, the patient who has taken oral antibiotic therapy is the most important concern in clinical practice. However, acute rhinosinusitis with viral etiology may be resolved without any treatment but bacterial rhinosinusitis is treated by antibiotics. The diagnosis of bacterial ARS may be considered when symptoms prolonged over 10 days or there is deterioration after drug-free follow-up period [3]. The guideline from the American Academy of Pediatrics [4] suggested that physicians must use antibiotic treatment for ARS in children with intense beginning or deteriorating progression. As well, reporters also advised that physicians should either use antibiotic therapy or offer further outpatient observation for 3 days to children with persistent disorder. This report also confirmed that if there is no improving in symptoms or if there is a failure to recover, clinicians should modify antibiotics or initiate antibiotics in child treated with observation [4]. The recommendation of using antibiotics for severe or worsening acute bacterial sinusitis in consequence of the benefits showed a theoretically higher risk of suppurative complications than for children who existed lasting symptoms.

It is recommended that when the clinical diagnosis of acute bacterial rhinosinusitis (ABRS) is established, empirical antimicrobial therapy should be initiated directly [5]. Amoxicillin-clavulanate (45 mg/kg/day, divided into two doses) instead of amoxicillin alone is recommended as the initial therapy of ABRS in children. The cephalosporins such as cefuroxime, cefdinir or cefpodoxime, clindamycin (or linezolid) + cefixime, and levofloxacin may be preferred in the condition of a penicilin allergy. Cephalosporins are usually used as the suitable treatment for ARS. Cephalexin and cefadroxil, which are the first-generation agents, are not the first choice for *H. influenzae* infection. Beta-lactamase-producing *M. catarrhalis* and some *H. influenzae* strains has reduce the response to cefaclor (50 mg/kg/day in two doses), and early second-generation cephalosporins. On the other hand, beta-lactamase-producing bacteria have a good response to second-generation cephalosporins (cefuroxime axetil, 30 mg/kg/day and cefprozil, in two doses as oral suspension). Third-generation cephalosporins such

as cefixime, ceftibuten, cefpodoxime axetil (10 mg/kg once daily), and cefdinir (14 mg/kg/day in one or two doses) seem to be an alternative option for the therapy. Macrolides (clarithromycin and azithromycin) are not recommended for empirical treatment due to elevated resistance rates of *S. pneumoniae*. Because of high resistance rates between *S. pneumoniae* and *Haemophilus influenzae*, trimethoprim-sulfamethoxazole is not recommended for empirical treatment. Ampicillin-sulbactam (100 mg/kg/day for three times a day) or ceftriaxone (100 mg/kg/day at single or double dose) given intravenously or intramusculary can be used in patients who do not endure oral antibiotics due to vomiting or in patients who do not recover after 24–48 hours of treatment with a second antibiotic therapy. If there is a suspicion of an aerobic pathogen as a cause of ARS, clindamycin or metronidazole may be added to a wide spectrum antibiotics. In patients with acute bacterial RS, the appropriate treatment duration is not definitively defined, but 10–14 days of treatment appear to be adequate for mild acute forms, but 14–21 days of treatment appear to be appropriate for severe acute forms and subacute forms [5].

2.2. Intranasal saline irrigation

Nasal saline irrigation has been shown to be effective and well tolerated in children with rhinosinusitis [6]. Management of sinus disease often involves the use of saline irrigations. Saline irrigation helps patients with rhinosinusitis by improving mucociliary clearance, slenderizing mucus, and providing anti-inflammatory effects [7]. Decreasing in symptoms after nasal irrigations is associated with an increase in quality of life in patients with acute rhinosinusitis [3, 8, 9].

2.3. Intranasal corticosteroids

It has been also shown that the use of intranasal corticosteroids significantly improved the symptoms of ARS [3]. Intranasal corticosteroids are recommended for both moderate (monotherapy) and severe (oral antibiotics) types of acute rhinosinusitis [10]. A double-blind, placebo-controlled trial revealed the efficacy of topical corticosteroid therapy in comparison with both monotherapy and antibiotics [11]. In this study, mometasone furoate (MF) was compared with amoxicillin and placebo in patients with ARS. MF 200 μg twice a day was significantly better than placebo and amoxicillin for correction of symptom score. MF was used once a day and was superior to placebo but not to amoxicillin. This study is the first study to show that topical corticosteroids are effective when given twice daily in the treatment of ARS and are more effective than amoxicillin. The results of this study were also supported by two other studies with a similar design. However, in another study, the use of antibiotics and topical steroids alone and in combination has not been effective in changing the severity of symptoms or duration of bacterial ARS. However, in this study, the patients with 4 days of symptoms and only those with colds and not ARS have been included. It is supported by the use of intranasal corticosteroids alone or as adjuvant therapy to antibiotics. High doses of intranasal corticosteroids (mometasone furoate 400 versus 200 μg) have a stronger effect on the reduction or complete improvement of symptoms. There was no significant adverse effect for both treatment groups, and there was no significant difference in the reduction in

symptoms and recurrence rates with higher doses of intranasal corticosteroids. Further randomized clinical trials are needed to examine the effectiveness and proper use of antibiotics and intranasal corticosteroids as a single or combined therapy for the treatment of different severe ARS. There are some studies comparing the effectiveness of mometasone furoate nasal spray and amoxicillin and placebo in patients with acute, uncomplicated RS. It is concluded that the use of mometasone furoate twice daily as 200 μg in acute, uncomplicated RS patients significantly reduced symptoms when compared with amoxicillin and placebo without predisposing factors or bacterial infection [12]. Rahmati et al. [13] revealed that the use of fluticasone in children has been associated with reducing the severity of acute sinusitis symptoms. Foden et al. [7] stated that intranasal corticosteroids (INCS) are the basis for the treatment of rhinosinusitis. As a monotherapy in ARS, INCS had a significant improvement in symptoms compared to placebo and amoxicillin [12]. On regarding the use of INCS, either as monotherapy or adjuvant to antibiotics, these studies have also been designed based on the approval of diagnosis. Intranasal corticosteroids (INCSs) are recommended in patients with a history of allergic rhinitis, especially as an adjunct to antibiotics for the empirical treatment of ABRS [5].

2.4. Other treatment modalities

It was accepted as a symptomatic treatment of viral upper respiratory tract infections with analgesic, antipyretic, and decongestant drugs (topical or systemic) [6]. Decongestants should be used with caution in pediatric patients because there is a small number of studies on the efficacy and side effects of decongestants. Concurrent use of decongestant and antihistamine in the treatment of pediatric upper respiratory tract infection and inflammation is still debated. In patients with ABRS, topical or oral decongestants and/or antihistamines are not recommended as adjuvant therapy (strong, low to moderate). Oral corticosteroids may be added to the treatment of cases with nasal polyposis or marked mucosal edema when the initial treatment is not received [14]. Antihistamines are useful in the case of accompanying acute bacterial RS and allergic RS because they reduce the inflammatory component and respond positively to antibiotics. Except the current allergic rhinitis, there is no indication for the use of antihistamines (both intranasal and oral) in the treatment of postviral ARS [10].

2.5. Nonresponsive patients

The patients who have worsened clinically during the first 72 hours or who have not recovered after 3–5 days of empirical antimicrobial therapy with a first-step agent should be evaluated for resistance pathogens, nontoxic etiology, structural abnormality, or other reasons for treatment failure (strong, low). In patients with suspected sinus infection who cannot respond to empirical antimicrobial therapy, cultures are recommended to be obtained with direct sinus aspiration rather than nasopharyngeal swab (strong, moderate). Endoscopic-guided cultures of medium meatus may be considered as an alternative in adults, but their reliability was not determined in children (weak, moderate). Nasopharynx cultures are not considered reliable and are not recommended for microbiological diagnosis of ABRS [5].

3. Medical management of pediatric chronic rhinosinusitis

3.1. Intranasal saline irrigation

Nasal saline irrigation should be considered as the primary therapeutic tool in CRS, even in the child age group, which is a long-term CRS [15–17]. Nasal saline lavage can significantly reduce chronic sinusitis symptoms, improve disease-specific quality of life, and be well tolerated in children with chronic rhinosinusitis symptoms [6, 18]. Nasal saline solutions make it easier to mechanically remove the mucus and increase the ciliary rhythm [19]. Nasal saline sprays or irrigations when tolerated are also used in the treatment of CRS, and primarily, sinonasal secretion, pathogens and debris removal are thought to help. Although Cochrane collection does not support any advice on nasal saline irritation, some studies have shown some degree of efficacy in CRS [16].

3.2. Intranasal corticosteroids

Topical steroids, although the absolute resolution of the CRS does not improve, may accelerate the solution of CRS symptoms when evaluated in the short term. In the management of CRS, it may be affected by suspected or proven allergic disease, including steroids. In particular, nasal steroids should be maintained when an allergic patient is treated for CRS. Topical nasal steroids suppress mucosal inflammation [9]. Examples include fluticasone propionate, commonly found in generic form, and mometasone furoate, which is indicated for use in nasal congestion due to allergic rhinitis in children aged 2 years and older. Topical nasal steroids are usually preferred for children with CRS due to low systemic bioavailability. Therefore, systemic side effects are rare in children with CRS and the most common complication is epistaxis. Although long-term prophylactic use often seems to be safe, it helps to suppress chronic symptoms and recurrent diseases, and typically conflicts with long-term antibiotic medicines used in CRS every 3–6 weeks [16].

3.3. Antibiotic treatment in the management of pediatric chronic rhinosinusitis

3.3.1. Oral antibiotics

Long-term and broad-spectrum antibiotics have been the basis for treating pediatric chronic rhinosinusitis. Amoxicillin/clavulanate is a good choice for first-line treatment, but antibiotics to be selected must also be effective against possible pathogens in CRS, including *S aureus*, Pseudomonas and anaerobes. Encompassing for MRSA may be indicated. Long-period treatment with macrolides for up to 12 weeks may also benefit patients with CRS. A culture should be obtained, preferably directly from the sinus cavity or endoscopic, in patients who do not recover or develop worsening despite treatment. For the last 20 years, antimicrobial resistance has been increasing. These contain the creation of beta lactamases and cephalosporins. Clindamycin can be administered in the event of penicillin allergy or who suspect MRSA. Other oral agents covering MRSA include trimethoprim-sulfamethoxazole and linezolid. The dose of amoxicillin-clavulanate recommended for children is 45 mg/kg. Another

recommended antibiotic management procedure is high-dose amoxicillin or amoxicillin/clavulanate (90 mg/kg/day orally twice daily) for children from environmental areas with high endemic degrees (>10%) of aggressive penicillin-nonsusceptible (PNS) *S. pneumoniae*. In addition, high-dose amoxicillin or amoxicillin/clavulanate therapy is recommended for the children with severe infection, attendance at nursery, age<2, latest hospitalization, antibiotic usage within the past month, and immunocompromisation [6, 16, 20]. Metronidazole can be administered in addition to one of the following antibiotics: cefazolin, cefuroxime, cefixime proksetil, clarithromycin, azithromycin, or trimethoprim-sulfamethoxazole and is administered as three times a day for 30–50 mg/kg/day and maximum daily dose for 2.250 mg/day. Antimicrobial therapy is given for a three-week period and can be extended up to 10 weeks in patients with antibiotic resistance [19].

3.3.2. Parenteral antibiotics

Parenteral treatment is applied to children who are extremely ill, who undergo surgery or who have a problem of adaptation to the oral regimen. Among the parenteral antimicrobials such as ampicillin-sulbactam, piperacillin-tazobactam, clindamycin, moxifloxacin, carbapenems (imipenem, meropenem, doripenem), and second-generation cephalosporins, cefoxitin effective against both anaerobes and aerobes are included. Vancomycin, linezolid, and daptomycin and ceftaroline are among the parenteral antimicrobials effective against MRSA. Metronidazole may be given as parenteral against anaerobes in combination with an agent with aerobic activity [9, 20].

3.3.3. Intranasal antibiotics

Although topical antibiotic treatment is not recommended in the best part of CRS cases, further studies should be required according to the initial findings. Demands about the combination potential with dose, treatment time, optimal treatment method, and other therapies carry on to be responded [9].

3.4. Systemic corticosteroids

Oral methylprednisolone has a good tolerance and offers additional benefit to treatment with antibiotics for children with CRS [21]. Combination treatment with systemic corticosteroids and antibiotics was established to be favorable in children (age between 6 and 17 years) with CRS whose management with at least three 10–14–day sequences of wide-spectrum antibiotics was unsuccessful. Minimal side effects may be seen. It was observed that children treated with corticosteroids plus antibiotics had meaningfully better declines in entire symptom and sinus CT scores compared with those given placebo plus antibiotics. Complete clinical healing observed more frequently and reverts within 6 months less commonly in the active management group. Moreover, Ozturk et al. [21] conducted a randomized trial comparing amoxicillin-clavulanate with and without methylprednisolone, and examined the advantage of addition of systemic corticosteroids to oral antibiotics for the management of CRS. Both management arms revealed progress compared with baseline with the steroid management being meaningfully more effective regarding dropping CT

scores and total rhinosinusitis symptoms, such as nasal obstruction, cough, and postnasal drainage [22].

3.5. Adjuvant medical treatments

Adjuvant medical treatment involving antihistamines and decongestants for pediatric CRS has been used widely with unconfirmed benefits. Oral antihistamines and decongestants may offer symptomatic advance; but the general period of the disease may not be affected. Moreover, the effects of antihistamines and decongestants on secretions and mucosa may undesirably affect the innate physiologic mechanisms of the sinuses and nose to cope with infection and inflammation [9, 16, 19].

3.6. Treatment for gastroesophageal reflux

It is not proved to use proton pump inhibitors (PPI) for pediatric CRS. The International Consensus Statement on Allergy and Rhinology: rhinosinusitis [23] summaries the facts about CRS and laryngopharyngeal reflux. It has set grade B evidence to prove the relationship between these situations but expresses that treatment guidelines or mechanistic trials are requiring. This statement further endorses to establish accurately diagnosing laryngopharyngeal reflux before starting PPI management in patients with difficult to treat CRS [24].

4. Medical management of adult acute rhinosinusitis

4.1. Nasal saline spray/saline irrigation

In the treatment of adult ABRS, there has been a recommendation of topical nasal saline irrigation with either isotonic or hypertonic form as a combined treatment. Saline sprays have an effect on reducing rhinitis symptoms. Also, it revealed a better sinus-related quality of life, decreased symptoms, and drug use with routine hypertonic nasal saline irrigation. No serious side effect has been determined with saline irrigation. When compared to isotonic saline, hypertonic saline treatment may have a better anti-inflammatory result and ability to subtilize mucous and rapidly recover mucociliary clearance [5, 25].

4.2. Intranasal corticosteroids

In the routine treatment of acute bacterial rhinosinusitis, intranasal corticosteroids (INCSs) are recommended as a supplement to antibiotics, especially in patients with allergic rhinitis [5, 12, 26]. Intranasal corticosteroids improved the symptoms and had only minor side events, consisting of headache, nasal itching, and epistaxis [25].

4.3. Antibiotic treatment

In acute bacterial rhinosinusitis, the most common determined pathogens are *S. pneumoniae or H. influenzae,* so the use of amoxicillin (with or without clavulanate) is commonly recommended

for empirical treatment in adult patients [25, 27]. On the other hand, Chow et al. [5] recommends amoxicillin-clavulanate rather than amoxicillin as empirical antimicrobial therapy for ABRS in adults. Also, it is recommended to use penicillin or amoxicillin for 7–14 days [10]. Macrolides (azithromycin and clarithromycin) are not recommended for initial therapy because of high rates of resistance to *S. pneumoniae*. By the way, trimethoprim-sulfamethoxazole is also not recommended for initial therapy due to high rates of resistance to both *S. pneumoniae* and *Haemophilus influenzae*. As an alternative treatment to amoxicillin-clavulanate for empirical therapy of adult ABRS, doxycycline may be chosen for being highly effective against airway pathogens and having superb pharmacokinetic/pharmacodynamics features [5].

Because of the inconstant proportions of resistance among *S. pneumoniae*, there is no recommendation for second- and third-generation oral cephalosporin antibiotics in the initial monotherapy of ABRS. Combined treatment with a third-generation oral cephalosporin (cefpodoxime or cefixime) plus clindamycin may be used as a second-line treatment for children from geographic regions with high endemic rates of penicillin nonsusceptible *Streptococcus pneumoniae* or for children with non-type I penicillin allergy. İt is strongly recommended that the use of doxycycline, levofloxacin, or moxifloxacin may be an alternative treatment for initial antimicrobial therapy in adults who are sensitive to penicillin. According to the up-to-date data, it is not a recommended routine antimicrobial coverage for *S. aureus* or MRSA for the initial treatment of ABRS, even though *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]) is a possible agent in ABRS, and 5–7 days' therapy is recommended for uncomplicated ABRS in adults [5].

*H. influenza*e can be highly resistant to amoxicillin and ampicillin [28]. Fluoroquinolones remain highly effective against both *H. influenzae* and *S. pneumoniae* [29]. Though the role of the fluoroquinolones is growing, these drugs are commonly recommended as second-line treatment, or as first-line treatment in patients with moderate illness who have had recent antimicrobial treatment, or for clinically moderate to severe disease patients [30, 31]. In these cases, another treatment option may be using high-dose amoxicillin/clavulanate (4 g/250 mg per day). High-dose amoxicillin with clavulanate treatment (2 g orally twice daily or 90 mg/kg/d orally twice daily) is recommended for adult patients with ABRS who have high risk of being infected with an amoxicillin-resistant organism. High-dose amoxicillin/clavulanate (4 g/250 mg per day) is recommended for severe infection, findings such as evidence of temperature of 39°C [102°F] or higher and trend of suppurative complications, age over 65 years, necessity of hospitalization, antibiotic usage within the last month, immunocompromisation and living in geographic regions with high endemic rates (>10%) of invasive PNS S *pneumoniae*. Alternative treatment choice of acute rhinosinusitis comprises of cephalosporins. Third-generation cephalosporins, such as cefdinir or ceftriaxone, are enough effective against *H. influenzae* but have much lower effectiveness against *S. pneumoniae* [27].

4.3.1. Penicillin-allergic patients

Though resistance rates of macrolide antibiotics to *H. influenzae* and *S. pneumoniae* are rising throughout the world, as first-line agents in patients with β-lactam allergies, they are still preferred [31]. For these patients, either a fluoroquinolone (levofloxacin or moxifloxacin) or doxycycline is recommended as another agent for initial antimicrobial treatment. For patients who

do not have penicillin allergy, fluoroquinolones are not considered as the first-line treatment of ABRS, because results are similar to amoxicillin-clavulanate, and side effects are seen higher [27].

4.4. Additional treatments

Clinicians may recommend analgesics, nasal saline, and/or topical intranasal steroids, for symptomatic relief of ABRS. Nonsteroidal anti-inflammatory agents or acetaminophen are generally adequate for facial pain related to ABRS [25].

4.4.1. Decongestants

4.4.1.1. Topical decongestants

There are no recommendation about topical and oral decongestants as combined therapy. Decongestants may offer short-term relief for nasal congestion. Xylometazoline or oxymetazoline is the frequently existing topical decongestants. They can be found in the form of drops or spray and act by contracting the sinusoids in the nasal tissues. After applying these agents intranasally, within 10 minutes, local vasoconstriction occurs. Their effects last up to 12 hours. Decreased nasal mucosal blood flow and mucosal clearance may cause this long effect: the topical nasal decongestants. Topical nasal decongestants have important side effects such as nasal mucosal irritation, dryness, or ulceration. Long-term use (>10 days) of topical nasal decongestants may cause tachyphylaxis and rhinitis medicamentosa (rebound swelling of the nasal mucosa). Therefore, the use of topical nasal decongestants must be limited to 10 days [5].

4.4.1.2. Oral decongestants

Phenylephrine, pseudoephedrine, and ephedrine are frequently used as oral decongestants. As they offer rapid relief on a short term, they are preferred commonly. When compared to topical nasal decongestants, oral decongestants have a lower effect on the nasal obstruction. Because they have no effect of rebound phenomenon, they may be preferred for a long term. After oral intake, nasal decongestion starts within 30 minutes and continues for up to 6 hours. Phenylephrine is the least effective agent among the oral decongestants. There are some side effects related to the oral decongestants such as nervousness, drowsiness, agitation, and arrhythmias. There are some risks that should be avoided to use oral decongestants in combinations with alcohol or some medications such as sedatives and monoamine oxidase inhibitors. For patients with stable hypertension, commonly, there is no noteworthy rise in blood pressure. However, careful use is recommended in patients with prostatic hypertrophy, glaucoma, or ischemic heart disease [27].

4.4.2. Topical anticholinergics

Topical intranasal anticholinergics, such as ipratropium bromide, are mainly preferred to stop symptom of rhinorrhea. On nasal congestion, sneezing and itching has no significant effect. Nasal irritation, burning, and dryness are the most common adverse effects followed by a headache, dry mouth and stuffy nose, etc. On mucociliary clearance, nasal mucosal alteration, and olfaction, they have no effect with long-term usage [25].

4.4.3. Antihistamines

For management of acute rhinosinusitis, no clinical trials recommend the use of antihistamines. First-generation antihistamines have the anticholinergic effects, and thus, mucociliary clearance may be impaired. On the other hand, second-generation antihistamines have no anticholinergic effect and are not recommended for acute rhinosinusitis [25].

4.4.4. Mucolytics

As a mucolytic agent, guaiphenesin is a frequently used for mucolysis. It is commonly preferred together with a decongestant drug. While it is used to thin the nasal secretions and increase drainage, trials evaluate the effects of placebo and guaiphenesin on ciliary beat frequency and nasal mucociliary clearance, and could not reveal any assessable impact [25].

4.4.5. Oral corticosteroids

When oral corticosteroid steroids are used as monotherapy for ABRS, there is no recommendation to use of systemic steroids for ABRS and they have no advantage over placebo. Among their adverse events, in mild condition, gastrointestinal complaints, nausea, and vomiting may also be seen. But the effects of these agents must take into account on the systems of glucose metabolism, bone turnover, and cardiovascular circulation [25].

5. Medical management of adult chronic rhinosinusitis without nasal polyp (CRSsNP)

5.1. Saline treatment

Nasal saline irrigations have beneficial effects and are accepted treatment modality as strong recommendation for chronic rhinosinusitis. Among the advantageous effects of saline are healing of symptoms and improving quality of life, increase in mucous clearance, improved ciliary activity, interruption and elimination of inflammatory mediators, biofilms and antigens, and protection of the sinonasal mucosa [25]. Nasal saline treatment has beneficial safety profile, no risk of systemic absorption, and well patient tolerance make it a potent long-term topical nasal therapy approach. Irrigation solutions may be either isotonic or hypertonic saline. High-volume (>200 mL) nasal saline irrigations in addition to other medical treatments is strongly recommended for CRS. Hypertonic nasal saline irrigations notably enhanced CRS-specific quality of life, symptom scores, and diminished drug usage. For establishing the hygiene, microwave decontamination of the irrigation bottles may be considered as a useful disinfecting method. It has been established that saline irrigation is superior to saline spray in throwing out secretions and enhancing the quality of life [23, 25].

5.2. Intranasal corticosteroids

It has been shown that the patients with CRSsNP benefited significantly from topical nasal steroids. The direct transmission of INCS to the sinuses has a greater impact. Patients with

previous sinus surgery have a favorable impact of INCS in comparison with nonsurgical patients. INCS have only slight side effects. Modern INCS have no additional clinical effectiveness than the first-generation INCS [23, 32].

5.2.1. Standard delivery (sprays)

The standard measured dose of INCS should be used in the treatment of CRSsNP. There is a significant improvement in the endoscopic and symptom scores. Dominance of benefit outweighs harm. Aggregated degree of evidence is A. Epistaxis and headache may be seen as side effects [23].

5.2.2. Nonstandard delivery (sprays)

Penetration of topical nasal sprays behind the nasal cavities into the paranasal sinuses, especially in preoperative patients, is expected to be limited. This situation caused a need to use of new delivery devices to offer improving corticosteroid deposition in the sinus tissues and for possible clinic healing. There are four prominent nonstandard delivery methods: (i) intranasal irrigation, (ii) maxillary antrostomy sinusotomy tubes (MAST), (iii) mucosal atomization devices (MAD), (iv) YAMIK sinus catheter. As a consequence, intranasal corticosteroid irrigations are the option in CRSsNP. They may be mostly beneficial for postoperative patients. The utilization of MAST or MAD is an option. Use of the YAMIK device is not recommended based on up-to-date data [23].

5.3. Oral corticosteroids

There is no clear evidence on the benefits of oral corticosteroids in CRSsNP. Oral steroid usage in CRSsNP is optional, due to inadequate strong evidence. Oral steroid use in perioperative period with CRSsNP is not recommended. The risks of oral steroids are uncommon, but significant side effects should be taken into consideration [10, 23, 33].

5.4. Antibiotics

5.4.1. Oral antibiotics

Sabino et al. [34] stated that 14 days of amoxicillin-clavulanate usage did not change any clinical course of acute exacerbations of chronic rhinosinusitis (AECRS) compared to placebo. Interestingly, combination of an oral antibiotic with a topical intranasal steroid spray may not offer further benefits for managing AECRS. When intranasal corticosteroids and saline irrigations have failed to reduce symptoms, long-term antibiotic treatment should be considered. Macrolide antibiotics have been used in the majority of trials. These antibiotics have revealed a response proportion of 60–80%. Roxithromycin has acceptable effects in patients without polyp. In a placebo-controlled azithromycin study, [35] suggests that the population with high serum IgE are less likely to respond to macrolide treatment. Long-term treatment with doxycycline or trimethoprim-sulfamethoxazole could reveal hopeful options. Level of evidence for macrolides in patients with CRSsNP is Ib, and strength of recommendation C, but in CRSsNP patients with normal IgE, the recommendation level is A [10].

5.4.2. Oral out of macrolide antibiotics for <3 weeks

When considering the use of antibiotic treatment less than 3 weeks in the management of CRS, current data are related to the treatment of AECRS. In addition, there is a shortage of suitable prospective trial at present. Because there is no sufficient clinical study and data, the ability to make recommendations regarding the use of nonmacrolide antibiotic for less than 3 weeks in CRSsNP is not applicable [10].

5.4.3. Oral out of macrolide antibiotics for >3 weeks

Although there are significant data on the role of long-term treatment with macrolide antibiotics for CRSsNP, there are little data in the literature concerning similar management with nonmacrolide agents. Dubin et al. [36] conducted an observational study with long-term oral antibiotics in patients with CRSsNP. Thirty five patients with CT scan and culture-approved CRSsNP were prescribed antibiotics for 6 weeks. At the end of the study, there was no considerable improvement between third and sixth weeks and only 38% of the patients reported improvement in CT scan scores. For the treatment of CRSsNP, the recommendation of nonmacrolide oral antibiotics for longer than 3 weeks has inadequate evidence. So, there is no applicable degree of evidence for the use of oral nonmacrolide antibiotics in CRSsNP [23].

5.4.4. Macrolide antibiotics

Macrolide antibiotics have both anti-inflammatory and antimicrobial functions, and for this reason, they may be considered to be effective in the treatment of CRS. Previous studies on lower respiratory diseases have led to be used macrolide antibiotics in the treatment of CRS. In those studies, erythromycin had been used in panbronchiolitis to improve clinical symptoms. Aggregated grade of evidence of these therapeutic agents is B. They offer, especially for patients without elevated IgE, a decline in endoscopy scores and some symptoms in patients with CRSsNP. Their effects are comparable to INCS. The effect of the agents may not sustain for long term after termination of treatment. They have important risks of drug interactions, in frequent mild undesirable events, and severe cardiovascular complications. Their benefits seem to outweigh harms. The convenient drug, dosage, and length of therapy are not recognized. Macrolides have an optional effect for patients with CRSsNP and were judged for the evidence of moderate quality [37].

5.4.5. Intravenous antibiotics

Intravenous antibiotics have a weak evidence in the treatment of CRSsNP. Their aggregated grade of evidence is C. There has been possible healing with patient-reported symptoms in case-controlled and cohort trials. Among their side effects, bleeding, deep vein thrombosis, drug adverse events, elevated liver enzymes, neutropenia, rash, thrombophlebitis, and sepsis may be determined. Their cost is high. The harm during the use of these agents outweighs the benefits. There is no recommendation for the use of intravenous antibiotics and should not be prescribed routinely in CRSsNP [23].

5.4.6. Topical antibiotics

The aim of topical antibiotic treatment for CRS is to transport high amounts of antibiotics into the sinonasal tissues, hence enhancing efficiency, diminishing systemic absorption and related side effects. It has been demonstrated that endoscopic sinus surgery increases the penetration of topical antibiotic agents from 2 to more than 95%. There is an aggregated grade of evidence of B for this management strategy, but randomized controlled trials have been unsuccessful to demonstrate any benefit from the application of topical antibiotic agents. Among their side effects, epistaxis, irritation, and nasal congestion may be seen. There is no recommendation regarding the topical antibiotic treatment in the management of CRSsNP at present [10].

5.5. Antifungal treatment in the management of adult chronic rhinosinusitis without nasal polyp (CRSsNP)

5.5.1. Topical antifungals

Physicians should avoid prescribing any topical antifungal therapy for routine patients with CRSsNP due to the systemic review of randomized controlled trials. Also, clinicians must avoid cost of ineffective therapy, unnecessary side effects, and shift of sinonasal flora [10].

5.5.2. Oral antifungals

For a significant subgroup of patients, fungi are considered as a causative agent of CRS with eosinophilic inflammation. Hence, it has been thought that antifungals have a possible effect in this subgroup of CRS patients. So, in the standard management of CRSsNP, there has been no confirmation about the use of oral antifungal treatment and aggregated grade of evidence is not applicable [10].

5.6. Combination treatment with nasal irrigation treatment in the management of adult chronic rhinosinusitis without nasal polyp (CRSsNP)

The antimicrobial effects of the sodium hypochlorite (NaOCl), particularly against *S. aureus* and *P. aeruginosa*, have been well established. Topical nasal irrigation with 0.05% NaOCl in saline solution has been found to be more effective than saline alone after 3 months usage [10, 38]. For nasal irrigation, xylitol in water is a well-tolerated substance. Xylitol irrigations lead to a further healing in chronic rhinosinusitis symptoms compared to saline irrigation [10]. It is considered that biofilms have the pathophysiological role in CRS. Surfactants have reductive effects on water surface tension and may facilitate dissolving of the biofilms. The use of sodium hypochlorite or xylitol nasal irrigations is supported by up-to-date with grade of recommendations B, but baby shampoo irrigations are not supported [10].

5.7. Proton pump inhibitors

There is no satisfactory evidence of the use for proton pump inhibitor therapy for CRSsNP in adults. Hence, there is also no support for the use of proton pump inhibitors, H2-receptor antagonists, antacids, or prokinetic therapy for chronic rhinosinusitis [39].

5.8. Topical alternative therapies

5.8.1. Surfactants

The benefits of surfactants are clearance of thick secretions and interruption of biofilm formation. Surfactants have the effects of clearance of secretions and blockage of biofilm development. Their side effects comprise ciliary dysfunction and nasal irritation. Although they have balanced effects regarding benefit and harm and limited clinical information, it is not possible to recommend for the use of surfactants in CRSsNP [23].

5.8.2. Manuka honey

Manuka honey and chief component methylglyoxal have in vitro effects against both the biofilm and planktonic formations of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. But, regarding the routine use of Manuka honey in CRSsNP, no clinical study exists. Possible respiratory epithelial damage, nasal irritation, and burning may also be seen. As of the lack of evidence, it is not possible to recommend to use Manuka honey in CRSsNP [23].

5.8.3. Xylitol

Xylitol is composed of five-carbon sugar and has the property of improving the innate immune system. The main effect of xylitol is to increase the activity of natural antimicrobial factors in respiratory secretions [23].

6. Medical management of adult chronic rhinosinusitis with nasal polyp (CRSwNP)

6.1. Saline (spray and irrigation) treatment

In the management of CRSwNP, saline is strongly recommended as grade A evidence. Both isotonic and hypertonic saline irrigations seem to offer similar subjective results and are well tolerated. There is a dominance of benefit rather than harm. It is important to use nasal saline irrigation in addition to other topical treatment approaches. There is a superiority of higher volume (>200 mL) irrigations over low-volume topical nasal sprays [10, 23, 40, 41]. Regarding the patients with difficult to treat sphenoid sinus disease, it has been suggested that the irrigation position of nose-to-ceiling head position is more effective than the nose-to-floor position in delivering a 120-mL irrigation to the sphenoid sinuses [42].

6.2. Intranasal corticosteroids: standard delivery (drops and sprays)

In the management of CRSwNP, the use of topical corticosteroids have keystone role. Intranasal corticosteroids (sprays or drops) are recommended before or after the surgery for CRSwNP. The use of INCS as sprays or drops have noteworthy benefits. Its advantages include improved symptoms, endoscopic views, size of polyp, quality of life, objective tests of smell, airway, and polyp relaps. Headache, epistaxis, and nasal mucosal damage may be seen as side effects [23, 40, 41, 43].

6.3. Intranasal corticosteroids: nonstandard delivery (irrigation and nebulizers)

Nonstandard topical corticosteroid delivery system, especially after sinus surgery, is an option in CRSwNP. General benefits are not available to statistically approve therapeutic recovery on existing evidence. Although evidence of adrenal suppression has not been seen, this cannot be ruled out by nonstandard delivery and dosing regimens. They have off-label use and possible minor side effects in comparison with oral corticosteroids [23].

6.4. Oral corticosteroids

The short-term oral corticosteroids usage in treatment of CRSwNP is strongly recommended. Both in subjective and objective measurements, this treatment provides a considerable short-term healing in the patients with CRSwNP. Patients must be prescribed systemic corticosteroids in acute aggravations of CRSwNP. The recovery time may take 8–12 weeks with the use of INCS. Further gastrointestinal complications may also be seen. There may be temporary adrenal inhibition, insomnia, and elevated bone turnover. With long-term management, the entire well-known corticosteroid complications may be seen. Corticosteroid agents have significant benefits over harm in short-term usage. The use of corticosteroids in long term or frequently is not encouraged by the literature and has further risk of damage to the patients [10, 33, 37, 40, 43].

6.5. Antibiotics

6.5.1. Oral out of macrolide antibiotics for <3 weeks

In general, there is no recommendation to prescribe nonmacrolide antibiotics less than 3 weeks course for the patients with nonacute clinic conditions of CrSWNP. Oral doxycycline therapy for 3 weeks decreases the polyp size and postnasal discharge, but this therapy cannot decrease the other complaints in patients with CRSwNP compared to the placebo. Because there is no placebo in the erdosteine study, it is impractical to establish a benefit. There may have gastrointestinal discomfort and risk of resistance and anaphylaxis. There may be more harm than benefits [10, 23, 40].

6.5.2. Oral out of macrolide antibiotics for >3 weeks

Long-term oral nonmacrolide antibiotics for more than 3 weeks course in the management of adult chronic rhinosinusitis with nasal polyp (CRSwNP) is not currently recommended [10, 23].

6.5.3. Macrolide antibiotics

Macrolides may have advantageous effects after endoscopic sinus surgery to reduce polyp recurrence and recover symptoms of CRSwNP. Benefits have shown outweigh harm. They may have considerable drug interactions. Also, they may cause infrequent but serious cardiovascular complications [10, 23].

6.5.4. Topical antibiotics

Topical antibiotic agents have efficiency in just lower stage studies and have unidentified systemic absorption and side-effect scale. So, they should be prescribed only if conventional management modalities (oral antibiotics, steroid sprays, saline) are unsuccessful [10, 23].

6.6. Antifungals

6.6.1. Oral antifungals

For the treatment of CRSwNP, there is no recommendation for prescribing oral antifungal agents. Liver function tests may be deteriorated during systemic usage. Because there is a lack of evidence for the use of oral antifungal therapy, there is a greater risk of adverse effects than potential advantages. For the usual management of CRSwNP, clinicians should not prescribe the oral antifungal drugs [10, 23].

6.6.2. Intranasal antifungals

For the usual CRSwNP treatment, topical antifungal medications should not be utilized. In the management of typical CRSWNP, there is no benefit of topical antifungals, but there may be some benefits in some CRSwNP subdivisions, such as allergic fungal sinusitis. Because they have unconfirmed systemic absorption and side-effect scale, topical antifungal agents should only be considered if routine treatment modalities failed [10, 23, 41].

6.7. Anti-LT therapy

For patients with CRSwNP, montelukast may be useful and an option to substitute or supplement to INCS. Symptoms can be improved when compared to the INCS and may have limited benefits in addition to the INCS. Montelukast is in association with infrequent neuropsychiatric side effects in post-sale records. In addition, there has been also in association with high liver enzymes and Zileuton and other medications [23]. On the contrary, anti-leukotriene treatment is not supported for the patients with CRSwNP and this treatment modality is not recommended [10, 23].

6.8. Aspirin desensitization

This therapy must be considered and recommended in patients with aspirin exacerbated rhinitis disease to impede postoperative nasal polyp renewal. The aggregated grade of evidence is B. Benefits include decreased polyp reformation after surgery, decreased CRS symptoms in increased QoL and AERD, reduced the need for systemic corticosteroids, and decreased number of reoperations. It is necessary to be vigilant for gastrointestinal bleeding. It should be noted that this treatment has the potential to increase morbidity in patients with kidney disease and blood clotting problems with the increasing doses. There has been lower than 3% gastrointestinal complaints throughout the low-dose treatments. Absolute benefit is present rather than harm. Aspirin desensitization is a unique treatment modality for aspirin-sensitive patients with CRSwNP [10, 23].

6.9. Immunotherapy

For postoperative period of AFRS patients, this treatment modality offers an option with balanced benefit and harm. There is a limited data and the grade of evidence is C. If a patient represents enhanced sensitivity to the certain antigens, immunotherapy may be used to diminish the inflammatory load [23, 40].

6.10. Anti-IL 4 and anti-IL13 treatment

An anti-IL-4/13α subunit receptor antibody, dupilumab, has been approved for atopic dermatitis [44]. Add-on therapy of dupilumab may have a role in nasal symptom relief for patients with uncontrolled persistent asthma and comorbid persistent allergic rhinitis [45]. It has been observed that for the patient with nasal polyp, addition of subcutaneous dupilumab to mometasone furoate nasal spray reduced endoscopic nasal polyp scores after treatment. More sophisticated studies are needed to evaluate for longer treatment duration and larger patient samples [46].

6.11. Anti-IL5

Reslizumab is an anti-IL5 mAb derived from human tissues and acts diminishing the amount of eosinophils both in tissue and blood. Anti-IL5 antibodies may have benefit in the management of CRSwNP patients [10].

Mepolizumab, FDA approved for severe eosinophilic asthma, is another anti-IL-5 human derived antibody that has been studied in patients with CRS. For the patients with recurrent nasal polyposis, who receiving topical corticosteroids and required surgery, mepolizumab treatment showed a huge reduction in the need for surgery and a huge improvement in symptoms than placebo [44, 47]. Also, there is a continued clinical trial of mepolizumab in the patients with CRSwNP refractory to medical and surgical therapy [48].

Benralizumab is another anti-IL5 molecule that could potentially have some benefits for inhibiting the IL-5 pathway in CRS [44].

6.12. Anti-IL13

Lebrikizumab did not substantially heal FEV1 in mild-to-moderate asthma patients by inhibiting IL-13 pathway. Inhibiting IL-13 in this patient population was not satisfactory to improve lung function [49].

Tralokinumab, an agent of anti-IL13, in severe asthma exacerbations, has not been considered as a key role for interleukin 13, and it was stated that Tralokinumab is unsuccessful for management of severe, uncontrolled asthma [50–52].

Anrukinzumab is a humanized anti-IL-13 monoclonal antibody, which acts to block the cytokine and prevent the activation of IL-13Rα1 and IL-13Rα2 [53, 54].

So far, there is no approved anti-IL13 treatment modality for the patients with CRwNP.

6.13. Anti IgE

Omalizumab is a human-derived anti-IgE monoclonal antibody that prevents binding of IgE to receptors on mast cells and basophils. Omalizumab has been approved for severe allergic asthma [44]. Anti-IgE therapy also reduces nasal polyp score in patients with severe comorbid asthma [55].

6.14. Intranasal triamcinolone acetonide/carboxymethylcellulose foam

For acute exacerbations of postoperative CRSwNP patients, it has been observed that topical triamcinolone acetonide/carboxymethylcellulose foam reduced systemic steroid need, is well tolerant, and a good treatment option [56].

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Chapter 5

Orbital Cellulitis

Lizette Mowatt

Additional information is available at the end of the chapter

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Abstract

Infection in the soft tissues of the orbit, posterior to the orbital septum results in orbital cellulitis. This is a very serious condition, which may occur as a complication of sinusitis by contiguous spread or may result from haematogenous spread or from trauma. Orbital cellulitis presents with periorbital swelling, proptosis, conjunctival chemosis and injection, extraocular motility deficits and visual loss. It requires comanagement by the ophthalmologist and otorhinolaryngologist when secondary to sinusitis. It is important that this condition is recognized early, and immediate management is done to prevent impending visual loss and further complications of periosteal abscesses, meningitis, cavernous sinus thrombosis and death. This chapter reviews the epidemiology of orbital cellulitis, pathogenesis, causative organisms, investigations (including imaging of the sinuses) and treatment. Prognostic factors and conditions that complicate this such as diabetes will also be discussed.

Keywords: orbital, sinusitis, periorbital swelling, proptosis, brain abscess, meningitis

1. Introduction

Orbital cellulitis is the involvement of the orbital tissues behind the orbital septum with inflammation or infection. The orbital septum is an important dividing landmark, as infection and inflammation occurring anterior to it is called preseptal cellulitis, which is managed differently than that occurring posterior to it, orbital cellulitis.

Orbital cellulitis is an inflammatory process and is generally used to describe infectious inflammation [1]. The sinuses are closely associated with the orbit and are commonly the source of infection from direct contiguous spread. It is important that orbital cellulitis is diagnosed, investigated with imaging to determine if the source is from the sinuses and treatment (medical and/or surgical) commenced early to prevent serious complications,

including cerebral abscess and meningitis. Sinus surgery may be required for the treatment of orbital cellulitis secondary to sinusitis or pansinusitis. The management of this condition may, therefore, require a multidisciplinary team of the ophthalmologist, otolaryngologist, infection specialist and neurosurgeon.

2. Orbital anatomy

The bony orbit is a pear-shaped cavity which houses the eyeball with its adnexae (lacrimal gland) and orbital fat. The volume of the orbit is ~30 ml of which the eyeball takes up 6 ml (20%). The orbit is related superiorly to the frontal sinus, inferiorly to the maxillary sinus, medially the ethmoid sinus and anterior aspect of the sphenoid sinus.

The anterior border of the orbit is the **orbital septum**, which separates the lid from the orbit. The orbital septum, a fibrous tissue arises from the periosteum of the superior and inferior orbital rims, divides the plane of the inflammation or infection into preseptal or postseptal (orbital cellulitis) (**Figure 1**). Infection anterior to the orbital septum is called preseptal cellulitis and can be managed by oral antibiotics. However, when the infection is posterior to the orbital septum, it results in orbital cellulitis which is an ophthalmic emergency requiring in hospital treatment.

The orbit is bounded superiorly by the **roof** (the lesser wing of the sphenoid bone and orbital plate of the frontal bone), which is below the anterior cranial fossa and frontal sinus. The greater wing of the sphenoid and the zygomatic bone make up the **lateral wall** (**Figure 2**).

Three bones make the **floor of the orbit,** the zygomatic, maxillary and palatine. Blow out fractures commonly occur in the posterior medial aspect of the maxilla. The orbital floor is also the superior boundary of the maxillary sinus.

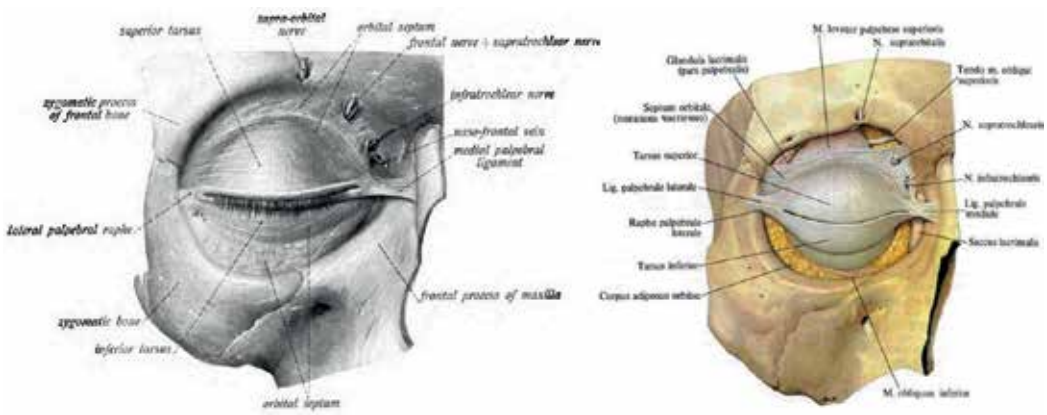

Figure 1. An anatomical illustration from the 1909 edition of Sobotta's Anatomy. https://commons.wikimedia.org/wiki/File:Sobo_1909_770.png#/media/File:Sobo_1909_770.png. Source: Riordan-Eva and Cunningham [2]. Copyright © 2018 McGraw-Hill Education. All rights reserved.

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Four bones make up the **medial wall**; maxillary (frontal process), lacrimal, ethmoid and sphenoid bone (**Figure 3**). The lamina papyracea, which forms part of the medial wall, is paper-thin and perforated by numerous foramina for nerves and blood vessels, which makes easy contiguous spread from the ethmoid sinuses to the orbit in the spread of orbital cellulitis.

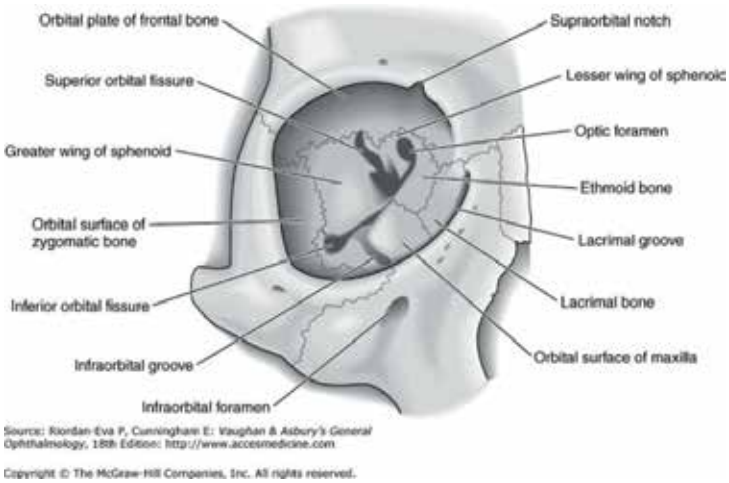

Figure 2. Anterior view of bones of right orbit. Source: Riordan-Eva and Cunningham [2]. Copyright © 2018 McGraw-Hill Education. All rights reserved.

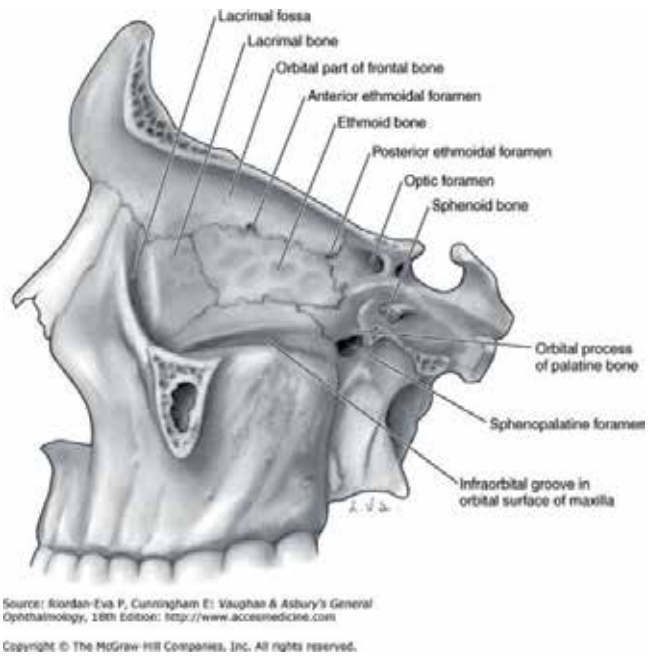

Figure 3. Medial wall of the orbit. Source: Riordan-Eva and Cunningham [2]. Copyright © 2018 McGraw-Hill Education. All rights reserved.

The **superior orbital fissure** is between the greater and lesser wings of the sphenoid and allows communication between the cranium and the orbit (**Figure 2**). This fissure is divided into the superior and inferior portion. The superior portion transmits the superior ophthalmic vein, lacrimal, frontal and trochlear nerves. The inferior portion transmits the abducens nerve, superior and inferior divisions of the oculomotor nerve and the sympathetic fibres from the cavernous plexus. Inflammation of the superior orbital fissure and orbital apex is called Tolosa-Hunt syndrome.

The **inferior orbital fissure** is located between the greater wing of the sphenoid and the maxillary bone, which divides the lateral orbital wall from the orbital floor (**Figure 2**). It connects the pterygopalatine and infratemporal fossae with the orbit and transmits the maxillary and zygomatic nerves in addition to the branches of the inferior ophthalmic vein.

The lesser wing of the sphenoid has the **optic foramen** through which the optic nerve and ophthalmic artery is transmitted from the middle cranial fossa to the orbit.

2.1. Epidemiology of orbital cellulitis

Orbital cellulitis may occur at all age groups but is more commonly seen in children. The incidence in children is 1.6 per 100,000 compared to adults 0.1 per 100,000 [3]. Gender distribution is usually equal; however, the males predominate in some countries because of work-related injuries as in India and Nigeria [1]. Orbital cellulitis has its peak incidence in winter and early spring [1, 4] and is least frequent (19.4%) in the summer months [5].

In the western countries, patients have an average duration of symptoms for 4.4 days and an average hospital stay of 5.8–6.2 days compared with developing countries, where the average symptom duration is 5.2–10.6 days, prior to presentation and have a longer average hospital stay of 9–13.7 days [1]. In developing countries, late presentation results in poor prognosis [6].

2.2. Pathogenesis of orbital cellulitis

Orbital cellulitis may result from direct contiguous spread (e.g. sinuses or dental), exogenous (e.g. trauma or surgery) and endogenous (haematogenous). Orbital cellulitis is unilateral in greater than 90% of cases [7]. Most cases of orbital cellulitis result from the extension of infection from the paranasal sinuses [1, 6]. Approximately, 1.3–5.6% of sinusitis results in orbital cellulitis and 80% of all complications of acute rhinosinusitis are orbital (**Table 1**) [4, 10–12].

The ethmoid sinuses are the most frequent source of infection in 43–100% of cases [1]. This may be due to the thin medial orbital wall. Other predisposing factors for the orbital spread include lack of lymphatics and valveless veins of the orbit and foramina of the orbital bones. Childhood orbital cellulitis may involve more than one sinus in 15.7–38% of cases, whereas in adults the multiple sinus involvement was <11%.

Upper respiratory tract infections are a major cause of orbital cellulitis and can reflect the seasonal distribution of the disease [1, 4]. Contiguous spread may also occur from endophthalmitis, pan ophthalmitis, dental abscesses and extension from preseptal cellulitis. Dental infections can result

Group	Chandler et al.	Moloney et al.
I	Preseptal cellulitis	Preseptal cellulitis
II	Orbital cellulitis	Subperiosteal abscess
III	Subperiosteal abscess	Orbital cellulitis
IV	Orbital abscess	Orbital abscess
V	Cavernous sinus thrombosis	Cavernous sinus thrombosis

Table 1. Classification of the complications of sinusitis by Chandler et al. [8] and modification by Moloney [9].

in odontogenic orbital cellulitis with spread through the maxillary sinus. Haematogenous spread from a bacteraemia may occur and a bilateral orbital cellulitis has been reported in a case of infective endocarditis [13].

Trauma is a predisposing factor, which may be a direct penetrating injury or orbital fractures. Orbital cellulitis may occur from direct spread from the sinuses as seen in trauma resulting in a blow-out fracture of the orbit. Orbital foreign bodies can be metallic or organic, with the latter (e.g. wood) containing significant bacteria [14]. Less commonly it has been reported after surgery usually with the use of an explant such as aqueous drainage device (glaucoma surgery) or silicone scleral sponges (retinal detachment repair) [15, 16].

2.2.1. Microorganisms

Staphylococcus aureus and *Streptococcus* species are the most common causative organisms [1]. There are increasing cases of methicillin resistant *Staphylococcus aureus* (MRSA). *Streptococcus pneumoniae* is seen more commonly in younger children and *Group A Streptococcus* in older children. In one study from Scotland, *Streptococcus* (66%) and *Haemophilus* (46%) were the most common pathogens in children [3]. Less commonly coagulase-negative *Staphylococcus, Haemophilus influenza, Klebsiella pneumoniae, Moraxella catarrhalis* and other respiratory tract anaerobes were implicated [17]. *H. Influenzae* used to be a common pathogen; however, this has significantly reduced after the introduction of the *H. influenzae* vaccine [17–19].

Post traumatic cases are usually due to *S. aureus* and *S. pyogenes. Streptococcus* infections can lead to a necrotizing lid disease and necrotizing fasciitis [1]. Trauma with penetration of organic foreign body may have *Staphylococcus epidermidis, Staphylococcus aureus, Enterobacter agglomerans and Clostridium perfringens* as the offending organisms [14]. Odontogenic infections resulting in orbital cellulitis usually have mixed aerobic and anaerobic bacteria.

Fungal infections are usually seen in high risk patients such as diabetes mellitus, immunocompromised patients, patients on chronic steroids or antibiotic treatment. Mucormycosis and aspergillosis are the most common types. Fungi can invade blood vessel walls causing a thrombosing vasculitis. This can cause significant severe complications of ophthalmic vascular thrombosis, cavernous sinus thrombosis, meningoencephalitis, brain abscess and ultimately a high mortality rate [1].

2.3. Clinical features

Orbital cellulitis presents with periorbital oedema and cellulitis of the eyelids, ptosis, red eye with conjunctival chemosis and pain on eye movements. As it worsens proptosis, reduced vision and double vision occur due to limitation of extraocular movements with the orbital swelling (**Figure 4**). Most common symptoms are reduction in vision (66.6%), proptosis and ptosis (33.3%) [12]. Patients may also experience pain on eye movements due to inflammation of the extraocular muscles. Patients may give a history of sinusitis or an upper respiratory tract infection.

Constitutional signs such as fever, malaise, loss of appetite are usually present. Headache may occur in 10% of patients. Children are more likely to have a fever and a higher leukocytosis [7]. Children less than a year may present with fever, periorbital edema and erythema with reduced appetite and lethargy [1]. Patients between 1 and 7 years old are less likely to have proptosis and ophthalmoplegia compared to older children and adults.

Clinical signs include proptosis, limitation of extraocular movements, reduced vision, a relative afferent pupillary defect (RAPD) and impaired colour vision. Compression of the central retinal artery can compromise vision from optic nerve ischemia with resulting infarction of the sclera, choroid and retina [7]. Secondary inflammation can result in iridocyclitis, vitritis and septic pan ophthalmitis. Increase in the intraocular pressure, glaucoma, due to the increased congestion of the episcleral vessels can further reduce the vision.

This patient requires urgent ophthalmic admission, imaging, commencement of intravenous (IV) antibiotics and monitoring. Colour vision and pupillary reactions should be monitored every 4–6 h, in addition to the proptosis with the Hertel exophthalmometer.

Increased inflammation and congestion in the orbit can result in an orbital apex syndrome. The pupillary reactions should be monitored for a RAPD which suggests an optic neuropathy secondary to an orbital apex syndrome. Patients with a RAPD, elevated intraocular pressures and complete ophthalmoplegia can develop permanent loss of vision in that eye if orbital pressure is not relieved urgently.

Figure 4. Right orbital cellulitis with periorbital swelling and proptosis.

Odontogenic orbital cellulitis can rapidly progress and cause blindness from a severe tense orbit, with resulting central retinal artery occlusion and ischemic optic neuropathy [20]. With increasing proptosis, corneal ulceration from exposure keratopathy may occur.

2.3.1. Special clinical scenarios

2.3.1.1. Fungal orbital cellulitis

This condition can be caused by the fungus of the order *Mucorales*, usually found in the soil among decaying organic matter [21]. *Rhizopus, Rhizomucor and Mucor* species are most common and are related to pathogenesis of vascular invasion with resulting thrombosis and necrosis of tissues. Elevated levels of iron and glucose in the serum are a predisposing factor [21]. Aspergillosis, caused by the fungus *Eurotiales*, genus *Aspergillus* can be non-invasive or invasive and is associated with vascular involvement and bony erosion, initially affecting the sinuses then spreading to the orbit.

Diagnosis is usually done by biopsy or culture and requires aggressive treatment with intravenous antifungals and may require orbital exenteration. Cases of non-invasive aspergillosis do not require orbital exenteration. Invasive aspergillosis has been reported to masquerade as giant cell arteritis, with symptoms of jaw claudication, scalp tenderness and weight loss [21]. The initial onset of fungal orbital cellulitis can be insidious then rapidly progressive, so a high index of suspicion must be present.

2.3.1.2. Rhino-orbital mucormycosis

This is a rare opportunistic infection caused by the fungi "Mucoraceae." This usually occurs in patients with immunosuppression and diabetic ketoacidosis but has been seen in patients with myelodysplastic syndrome, chronic hepatitis C infection, polysubstance abuse, alcoholic liver cirrhosis and Crohn's disease with systemic immunosuppression [21]. Uncontrolled diabetic ketoacidosis is the most commonly associated condition in orbital mucormycosis.

Patients may present with gradual onset of facial and periorbital swelling, double vision and loss of vision. Septic necrosis can cause black eschar from ischemic infarction on the palate, turbinates, skin and eye lids. Complications can result in retinal vascular occlusion, cranial palsies and cerebrovascular occlusion. The onset may be insidious in immunosuppressed patients and a high index of suspicion must be present to prevent the delay in diagnosis and treatment.

Fungal infections can be acquired from inhalation of spores with resulting upper respiratory tract infection then sinus involvement, orbital cellulitis with contiguous spread to the brain. Mucormycosis initially involves the maxillary and ethmoid sinus, thereafter spreading to the orbit and brain. The severity of the hyphae invasion of blood vessels results in an occlusive vasculitis with ischemia and infarction of orbital tissues, which can eventually become fatal.

Fungal orbital cellulitis from aspergillosis has been reported in a patient with myelodysplastic syndrome and portal hypertension, with the initial presentation mimicking giant cell arteritis [21]. Gradual onset of periorbital and facial swelling, diplopia and visual loss may occur. Black

eschar results from ischemic infarction and septic necrosis of the palates, turbinates, nasal septum and eyelids and may present with ophthalmoplegia. The progression is slower than bacterial orbital cellulitis.

High risk of mortality is associated with bilateral orbital involvement, diabetes, renal transplantation with immunosuppression, leukaemia and hemiparesis [21]. A rare case of spread from a fungal nasal septal abscess *Scedosporium apiospermum* resulting in an orbital apex syndrome has been reported in a diabetic patient, which resulted in blindness [22]. Mucormycosis in immunocompetent patients is rare, and there has only been one reported case of zygomycetes infection in an immunocompetent child [23].

2.3.1.3. Allergic aspergillosis sinusitis

Allergic aspergillosis sinusitis occurs in immunocompetent patients who have nasal polyposis and chronic sinusitis. About 17% of allergic fungal sinusitis will present as orbital cellulitis. Patients will have an eosinophilia, with thick mucin in the sinuses on CT scans. Sinus biopsy reveals peanut butter like mucus with eosinophils and extra-mucosal fungal hyphae. Endoscopic debridement of the sinuses, treatment with corticosteroids is recommended [24].

2.3.2. Investigations (bloods and swabs)

Patients with orbital cellulitis require in hospital management. Blood investigations include full blood count. The leukocytosis is usually over 15,000 cells/microliter. Erythrocyte sedimentation rate (ESR) and blood cultures should also be done. Blood cultures are infrequently positive.

Conjunctival swabs and blood cultures usually have a low yield and may not be representative of organisms causing an orbital abscess. If meningeal or cerebral signs develop a lumbar puncture may be indicated to rule out intracranial complications in additional to imaging.

When fungal orbital cellulitis is suspected, intranasal biopsies sent for frozen section looking for hyphae elements can be helpful [21]. Diagnosis is confirmed by biopsy by the necrotic tissues in the nasopharynx or involved sinus. Zygomycosis has non-septate large branching hyphae that stain with hematoxylin-eosin stain. Aspergillus species stain with the Grocott-Gomori methenamine-silver nitrate showing septate branching hyphae of uniform width.

2.3.3. Investigations (imaging)

The most commonly affected sinus is the ethmoid (91.6%) (**Figure 5**) [12]. X-rays of the sinuses can show fluid-filled cavities in the sinus and may show thickened mucous membranes. However, CT scan imaging of the orbit and sinuses is the usual modality of choice for diagnosis and monitoring as it shows more definition. It is indicated in inflammation with proptosis, external ophthalmoplegia and reduced vision. Other indications include no improvement or deterioration of the patient's condition within 24 h or non-resolving pyrexia over 36 h.

The CT scan demonstrates the sinuses involved and size and location of possible orbital abscesses (**Figures 5** and **6a**, **b**). Sinus X-ray can show an air-fluid level, for orbital abscesses with gas [25]. Ultrasound can detect abscesses of the anterior orbit with 90% accuracy [6].

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CT scans have additional benefits as it also determines the inflammatory changes in the orbit and identifies potential sources of infection including a foreign body. It defines size and location of an orbital abscess and subperiosteal abscesses (**Figure 7**). Early abscesses may appear as increased soft tissue density and when enlarged, a fluid collection with rim enhancement may be present. Identification of orbital abscesses can be challenging on CT and a third of abscesses may be missed if the coronal sections are not done [26]. Contrast media can enhance

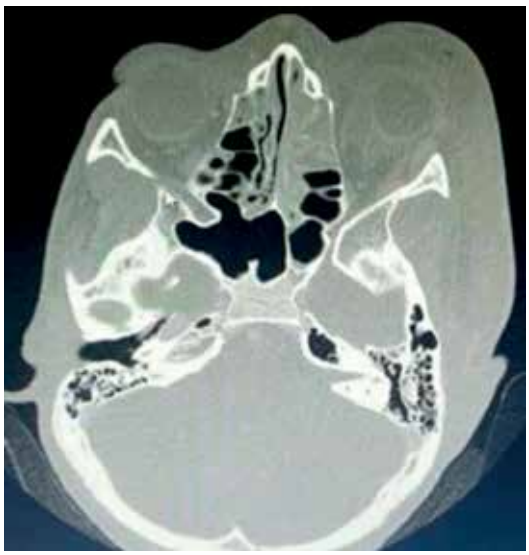

Figure 5. Left orbital cellulitis secondary to a left ethmoiditis with left periorbital oedema and associated mucosal thickening in the right ethmoid sinus (axial CT scan).

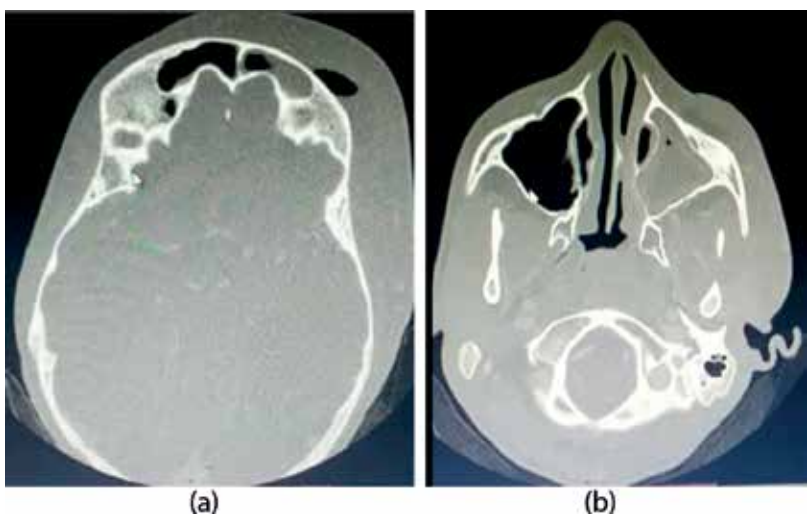

Figure 6. (a) Axial CT scan showing left frontal sinusitis associated with swelling of the left side of the face and air in the soft tissues. There is associated mild mucosal thickening in the right frontal sinus. (b) Axial CT scan showing left maxillary sinusitis.

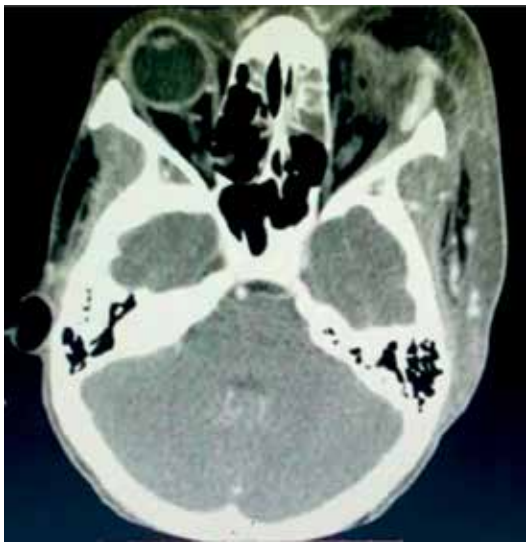

Figure 7. CT scan of the orbits showing air present in a localized loculated collection in the superior orbit.

the surrounding wall of the abscess on CT scanning and can differentiate between an abscess and orbital inflammation. The orbital abscess size may increase during the first few days of intravenous antibiotics [26].

The presence of neurological signs requires imaging for intracranial extension. MRI imaging can supplement CT scans with better resolution of orbital soft tissues. Fat saturated T2weighted MRI and diffusion weighted imaging are helpful. MRI is superior to CT for imaging orbital and subperiosteal abscesses and intracranial involvement and reduces the exposure to radiation [6]. In cases with possible complications, a MRI or CT venogram can help elucidate the presence of a cavernous sinus thrombosis.

2.4. Treatment

Orbital cellulitis requires in hospital management with intravenous broad-spectrum antibiotics. This should cover most Gram-positive and Gram-negative bacteria. Treatment of the predisposing factor, for example sinusitis, should be implemented early. Treatment is initially with 1–2 weeks of intravenous antibiotics followed by 4 weeks of oral antibiotics [4]. Management of these cases is multidisciplinary with involvement of the ophthalmologist, otolaryngologist, infectious disease and neurosurgical specialists.

Nasal decongestants help to promote spontaneous drainage of the infected sinus and early intervention to drain the involved sinus.

2.4.1. Antibiotics

Broad spectrum intravenous antibiotics are used empirically. In a Canadian study on orbital cellulitis in children, the commonest combination was IV cefuroxime (24%), IV clindamycin +

IV cephalosporin (21%) and IV cloxacillin + IV cefotaxime (18%) [17]. Subperiosteal abscess were noted in 31.5% of patients but only 21% of patients required surgical intervention [17]. In adults, high dose IV {Augmentin (amoxil and claviolonic), ceftriaxone and sulbactum} and metronidazole have been found to be effective [12].

Children have simpler infections than adults with one aerobic pathogen [7]. Children, 9 years and older and adults may have multiple aerobic and anaerobic organisms which may require medical and surgical treatment. There is a sliding scale of risk and older patients should undergo sinus surgery early before the development of orbital or intracranial abscesses.

CT scans are not predictive of clinical course for orbital abscesses [7]. Expansion of an abscess on CT scan in the first few days is not indicative of failure of antibiotics [26]. However, if visual function is compromised, drainage of the abscess is warranted. Drainage within 24 h is recommended if the orbital abscess is large (superior or inferior), dental involvement (children >9 years), evidence of intracranial extension, involvement of the frontal sinuses [7]. Children <9 years can be monitored with an expectant approach if they have a medial subperiosteal abscess (modest size), no visual loss, nor intracranial or frontal sinus involvement [7]. The patient must undergo continual monitoring of their optic nerve function (Snellen vision, RAPD, colour vision, pupillary reactions) and level of consciousness.

Fungal cellulitis requires aggressive antifungal treatment and may require orbital exenteration and yet still have a high mortality rate [21]. The treatment regime for fungal orbital cellulitis involves:

- Intravenous (IV) amphotericin and irrigation of amphotericin
- Aggressive surgical debridement -Wide excision of devitalized and necrotic tissues
- Adjunctive hyperbaric oxygen
- Correction of metabolic defect
- Exenteration in severe unresponsive cases.

Orbital fungal cellulitis is treated with intravenous anti-fungal. Intravenous amphotericin B can be used initially then posaconazole orally when discharged. Voriconazole or amphotericin B can be used for invasive aspergillosis. In mucormycosis, intravenous amphotericin B may be used or IV micafungin as an adjunctive treatment. In some cases, a suture tarsorrhaphy (closure of the eye lids) can be done and an irrigation cannula placed to deliver intraorbital amphotericin B [21].

Intra orbital catheter delivery of amphotericin B can be used as an adjunctive therapy with early aggressive surgical debridement when required. For invasive aspergillosis, voriconazole or amphotericin B may be used. The onset of fungal orbital cellulitis can initially be insidious then progress rapidly, so a high index of suspicion is important.

2.4.2. Surgical treatment

Approximately, 12–15% of patients require surgical management [5, 27]. Children 10–19 years old were more likely to require surgical intervention and much older patients with leukocytosis

[5]. The presence of acute and chronic sinusitis, proptosis, diplopia, conjunctival chemosis increases the odds ratio of surgical intervention.

Surgical treatment is used for treatment of the source of infections (pan sinusitis) and complication of orbital cellulitis (intraorbital or intracranial) with good result (**Figure 8a** and **b**). Drainage of a subperiosteal abscess requires an incision to the periosteum. Insertion of a drain for several days may be used. Functional endoscopic sinus surgery (FESS) can be done for some periosteal abscesses, eliminating the need for an external ethmoidectomy and facial scar [4]. In fungal orbital cellulitis, early diagnosis and initiation of treatment may also require limited debridement. However, severe invasive fungal orbital cellulitis may require exenteration.

2.4.3. Role of corticosteroids

Oral steroids may be used with caution as an adjunct to intravenous antibiotic therapy, as it can hasten the resolution of the inflammation, reducing the duration of the intravenous antibiotics and length of the hospital stay. It also has a low risk of exacerbating infection [28]. Steroids are started after a positive response to intravenous antibiotics has occurred [28]. Children with orbital cellulitis treated concurrently with intravenous steroids (IV dexamethasone 0.3 mg/kg/d Q6H for 3 days) had significantly shorter hospital stays than those without (3.8 vs. 6.7 days, $p < 0.001$) [29]. A short course of systemic steroids concurrent with IV antibiotics appears to be safe and efficacious [29]. The hospital stay was shorter for the children who had IV steroids, whether they had surgical intervention.

2.5. Complications

Complications from orbital cellulitis can result from mechanical factors in the orbit or haematogenous and contiguous spread. There are valveless veins around the orbit which predispose to this spread.

Ocular complications result from proptosis and increased pressure in the orbit. It includes exposure keratopathy, glaucoma, central retinal artery or vein occlusion, optic neuropathy from an orbital apex syndrome.

The other complications of orbital cellulitis include subperiosteal abscess, intracranial complications (cavernous sinus thrombosis, meningitis and brain abscess) [12]. Approximately, 0.3–5.1% develop orbital or subperiosteal abscess [10, 11]. Development of orbital abscess does not correlate specifically with the patient's vision, proptosis or any other sign [25].

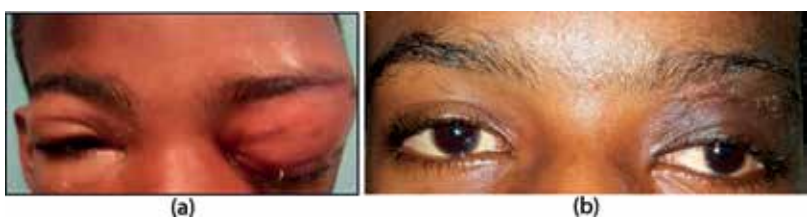

Figure 8. (a) Left orbital cellulitis. (b) Six weeks post-surgical intervention and intravenous antibiotics.

Orbital or periosteal abscesses should be suspected in patients with progressive proptosis with globe displacement, swinging pyrexia and failure to improve despite intravenous antibiotics. They are usually localized adjacent to the affected sinus in the subperiosteal space, usually the medial orbital wall. Serial imaging may be required.

In younger children <9 years, they may develop isolated medial or inferior subperiosteal orbital abscesses with good vision and mild to moderate proptosis, however, may settle with medical treatment.

Indications for surgical intervention for subperiosteal abscess [30] are:

- Patients ≥9 year old
- Non-medial location of subperiosteal abscess
- Involvement of frontal sinusitis
- Large subperiosteal abscess
- Suspicion of anaerobic infection
- Chronic sinusitis
- Acute optic nerve compromise
- Infection of dental origin

Orbital abscess is more likely in post-traumatic or post-operative cases. Before antibiotics, death from **meningitis** occurred in 17% of cases and blindness in 20% [8]. Present day, ~ 1.9% of patients will develop meningitis and 7–23% can result in blindness, from ocular complications such as corneal ulcer, central retinal artery occlusion or optic atrophy. Delay in required surgical intervention also results in a poor prognosis [8].

Orbitocranial complication of acute sinusitis in children, though uncommon can be life threatening causing high morbidity if diagnosed late. They may require additional procedures such as endoscopic sinus surgery, orbital decompression or subdural empyema drainage [31].

Intracranial complications are uncommon but can be very serious. Meningitis, brain abscess and cavernous sinus thrombosis can occur. Brain abscesses must be considered in patients who have the classic triad of headache, fever and neurological deficit, but may be present in <50% of cases, however, a headache may be present in 70% of cases [30, 32]. The neurosurgical team must be involved as neurosurgical drainage may be required. Cavernous sinus thrombosis must be considered in patients with rapid progression of proptosis, ipsilateral ophthalmoplegia. These patients may also have clinical signs of severe headache, nausea and vomiting. Orbital cellulitis is an inflammatory and infective disease of the orbit which can have visual threatening and life-threatening complications. It is important to diagnose, investigated and treat early to reduce complication and morbidity.

Conflict of interest

The author has no conflict of interest.

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Chapter 6

Sinonasal Cancers: Diagnosis and Management

Deepti Sharma, Neha Sharma and Vivek Sharma

Additional information is available at the end of the chapter

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Abstract

Sinonasal cancers are rare tumors constitute 3% of head and neck cancers. These include malignancies of the nasal cavity and paranasal sinuses (maxillary sinus, ethmoid sinuses, frontal sinus and sphenoid sinus). Patients are often asymptomatic until late in the course of their disease. Tumors of the maxillary sinus are more common than those of the ethmoid sinus or nasal cavity. The workup for patients with suspected paranasal sinus tumors includes complete head and neck CT/MRI with contrast. FDG-PET/CT may be considered in the workup of patients with clinically apparent stage III or IV disease. The most common histology for these tumors is squamous cell carcinoma, others reported includes adenocarcinoma, esthesioneuroblastoma, minor salivary gland tumors, or sinonasal neuroendocrine carcinoma [SNEC]). Surgical resection for all T stages (except T4b, any N) followed by postoperative therapy remains a cornerstone of treatment. However, definitive RT or systemic therapy/RT is recommended for T4b, any N. Locoregional control and incidence of distant metastasis are dependent on T stage, N stage, and tumor histology.

Keywords: sinonasal cancers, radiotherapy, surgery, maxilla, ethmoid

1. Introduction

Para-nasal sinuses are small air filled cavities occupying the facial and skull bones and along with nasal cavity, they form a small anatomical space but they are site of origin of histologically diverse group of tumors. These incorporate neoplasms derived from mucosal epithelium, seromucinous glands, soft tissues, bone, cartilage, neural/neuroectodermal tissue, haematolymphoid cells and the odontogenic apparatus.

2. Epidemiology

Nasal cavity and paranasal sinus cancers are a group of rare cancers, representing about 5% of all head and neck (H and N) cancer patients. They have an incidence of about 1 case every 100,000, with an average age between 50 and 60 years [1]. About 60% of sinonasal tumors originate in the maxillary sinus, 20–30% in the nasal cavity, 10–15% in the ethmoid sinus, and 1% in the sphenoid and frontal sinuses [2]. The incidence of cancer of the nasal cavity and paranasal sinuses (sinonasal cancer) is low in most of the populations (<1.5/100,000 in men and <1.0/100,000 in women), although higher incidence is seen in Japan and certain parts of China and India [3, 4]. Sinonasal squamous cell carcinoma and intestinal-type adenocarcinoma occur more commonly in men, with a male-to-female ratio of 2:1 in sinonasal squamous cell carcinoma, and up to 6:1 in intestinal-type adenocarcinoma [4, 5].

3. Anatomy

The paranasal sinuses are named according to the bones in which they are located: the ethmoid, maxilla, sphenoid, and frontal (**Figure 1**) [6].

3.1. Ethmoid complex

This paired complex of sinuses contains 3–18 cells that are grouped as anterior, middle, or posterior, according to the location of their ostia. The *posterior group* drains into the superior meatus above the middle nasal concha; sometimes one or more opens into the sphenoidal

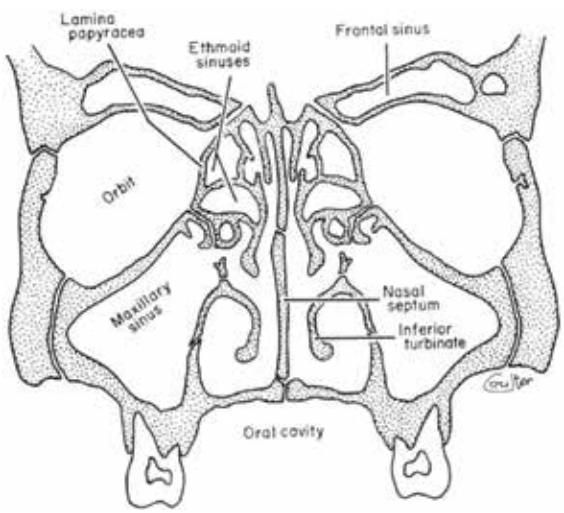

Figure 1. A schematic illustration of the relationship between the eye and the paranasal sinuses. The roof of the orbit, the medial wall, and the floor are shared by the frontal, ethmoid, and maxillary sinuses, respectively.

sinus. The *middle group* into the middle meatus of the nose on or above the bulla ethmoidalis and the *anterior group* drains into the middle meatus of the nose by way of the infundibulum.

Since ethmoid sinus is a paired structure, it is connected in midline by cribriform part of ethmoid bone, which also separates it from anterior cranial fossa. Direct extension of the tumor through cribriform plate causes involvement of frontal lobe. A pointed bony landmark called crista galli stretches out from the midline of the cribriform plate upward into the floor of the anterior cranial fossa. The perpendicular plate of the ethmoid bone descends from the cribriform plate forms superior two thirds of the nasal septum. Middle, superior, and supreme turbinates originate from medial wall of each ethmoid labyrinth. Lamina papyracea forms the thin lateral wall, separating the ethmoid cells from the orbit. It forms an easy conduit for tumor spread from ethmoid sinus to orbit. The fovea ethmoidalis is a segment of the ethmoid bone and represents its superior portion which is seen as a continuation of the superior orbital roof to the cribriform plate.

3.2. Maxillary sinus

The maxillary sinus is the largest sinus occupying the body of the maxillary bone. The sinus is pyramidal in shape and has three recesses. The alveolar recess lies inferiorly, the zygomatic recess pointing laterally and the infra-orbital recess pointing superiorly. The floor is formed by the alveolar process of the maxilla. The roof is formed by floor of the orbit. It is traversed by infraorbital nerves and vessels. The base of the maxillary sinus forms the inferior part of the lateral wall of the nasal cavity. Anterior wall of the pterygopalatine fossa, also known as the sphenopalatine fossa, forms posterior wall of the maxillary sinus. The anterior sinus wall is the facial surface of the maxilla that is perforated by the infraorbital foramen below the orbital rim. The maxillary sinus drains into the middle meatus by means of the semilunar hiatus. The floor of the maxillary sinus is slightly below the level of the nasal cavity, and it is related to the upper teeth [7].

3.3. Sphenoid sinus

Sphenoid sinus is a paired structure that lies in the body of sphenoid bone. They may vary in size and are usually asymmetrical, attributable to the parallel dislocation of the mediating septum. The relationship of the posterior extension of the sphenoid in relation to the sella turcica is variable. With the exception of the sinus roof, the other sinus walls are of variable thickness depending on the degree of pneumatization. The sphenoid sinus is related superiorly to cavernous sinus, sella turcica and its contents, inferiorly to nasal cavity and posteriorly to nasal cavity and posterior ethmoidal cells. Posteriorly it is related to middle cranial fossa and laterally to cavernous sinus and cranial cavity [7].

3.4. Frontal sinus

They are paired structures located between the inner and outer tables of the frontal bone. Each opening into the anterior part of the corresponding middle nasal meatus of the nose through

the frontonasal duct. Medially associated with the contralateral frontal sinus, Superiorly, laterally and posteriorly with the frontal bone and frontal lobe and Inferiorly with the orbit [7].

4. Etio-pathogenesis

4.1. Etiology

The etiologic factors vary by tumor type and location. Occupational exposures to wood and leather dust have been strongly associated with sinonasal cancers [7]. The risk of developing sinonasal cancer also increases with exposure to formaldehyde, in the textile industry and to nickel/chromium compounds [8]. Adenocarcinomas have been associated with wood dust, leather dust, and formaldehyde [9]. The risk is strongest in cases of adenocarcinomas and in sinonasal malignancies. The impact is present after 40 or more years since first introduction and persists after discontinuation. Squamous cell carcinomas have been linked to arsenic and welding fumes [10].

High relative risks of sinonasal cancers (SNC) have been observed for specific chemical exposures and occupational settings, including farming, construction, miners, drillers, blasters, plumbers, machinists, bakers and pastry confectioners, metal industry (chromium and nickel compounds) [11–14]. In contrast to most head and neck cancers, tobacco smoking does not seem to have a key role in the development of sinonasal tumors; nevertheless, evidence suggests that smoking tobacco can increase the risk of SNSCC twofold to threefold [1].

4.2. Pathogenesis

Several studies have established a causal role of exposure to hard wood dust and leather in the development of sinonasal cancer. Wood dust is a complex mixture of organic and inorganic components, including genotoxic and carcinogenic factors [15]. Its capacity to induce DNA damage has been attributed in part to its particulate nature, which induces the generation of reactive oxygen species in the cells. Several studies have established a causal role of exposure to hard wood dust and leather in the development of sinonasal cancer, with particular association with intestinal-type adenocarcinoma.

Molecular alterations seen in intestinal-type adenocarcinoma (ITAC) mainly focused on TP53, K-ras and H-ras gene mutations and EGFR or HER2 over-expression. Ras genes were found to be mutated only in rare cases, with conflicting reports about a possible prognostic role [16]. EGFR and HER2 are over-expressed in about 30% of cases [17]. The rate of TP53 mutations in intestinal-type adenocarcinoma is about 60% and it is significantly higher than in squamous cell carcinomas; TP53 mutation rate in ITAC is directly correlated with duration, average and cumulative level of wood dust exposure [18].

In a study by Chernock et al. (81.8%) were diffusely positive for c-KIT, 27.3% cases were positive for EGFR, but none of the cases were positive for HER2/neu [19]. In contrast, in a

Malignant epithelial tumors

- Squamous cell carcinoma
  - Verrucous carcinoma
  - Papillary squamous cell carcinoma
  - Basaloid squamous cell carcinoma
  - Spindle cell carcinoma
  - Adenosquamous carcinoma
  - Acantholytic squamous cell carcinoma
- Lymphoepithelial carcinoma
- Sinonasal undifferentiated carcinoma
- Adenocarcinoma
  - Intestinal-type adenocarcinoma
  - Nonintestinal-type adenocarcinoma
- Salivary gland-type carcinomas
  - Adenoid cystic carcinoma
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma
  - Epithelial-myoepithelial carcinoma
  - Clear cell carcinoma N.O.S.
  - Myoepithelial carcinoma
  - Carcinoma ex pleomorphic adenoma
  - Polymorphous low-grade adenocarcinoma
- Neuroendocrine tumors
  - Typical carcinoid
  - Atypical carcinoid
  - Small cell carcinoma, neuroendocrine type

Benign epithelial tumors

- Sinonasal papillomas
  - lnverted papilloma
  - (Schneiderian papilloma, inverted type)
  - Oncocytic papilloma
  - (Schneiderian papilloma, oncocytic type)
  - Exophytic papilloma
  - (Schneiderian papilloma, exophytic type)
- Salivary gland-type adenomas
  - Pleomorphic adenoma
  - Myoepithelioma
  - Oncocytoma

Soft tissue tumors

- Malignant tumors
  - Fibrosarcoma
  - Malignant fibrous histiocytoma
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Angiosarcoma
  - Malignant peripheral nerve sheath tumor
- Borderline and low malignant potential tumors
  - Desmoid-type fibromatosis
  - Inflammatory myofibroblastic tumor
  - Glomangiopericytoma
  - (Sinonasal-type haemangiopericytoma)
  - Extrapleural solitary fibrous tumor
- Benign tumors
  - Myxoma
  - Leiomyoma
  - Haemangioma
  - Schwannoma
  - Neurofibroma
  - Meningioma

Tumors of bone and cartilage

- Malignant tumors
  - Chondrosarcoma
  - Mesenchymal chondrosarcoma
  - Osteosarcoma
  - Chordoma
- Benign tumors
  - Giant cell lesion
  - Giant cell tumor
  - Chondroma
  - Osteoma
  - Chondroblastoma
  - Chondromyxoid fibroma
  - Osteochondroma (exostosis)
  - Osteoid osteoma
  - Osteoblastoma
  - Ameloblastoma
  - Nasal chondromesenchymal hamartoma

Haematolymphoid tumors

- Extranodal NK/T cell lymphoma
- Diffuse large B-cell lymphoma
- Extramedullary plasmacytoma
- Extramedullary myeloid sarcoma
- Histiocytic sarcoma
- Langerhans cell histiocytosis

Neuroectodermal

- Ewing sarcoma
- Primitive neuroectodermal tumor
- Olfactory neuroblastoma
- Melanotic neuroectodermal tumor of infancy
- Mucosal malignant melanoma

Germ cell tumors	Secondary tumors
• Immature teratoma	
• Teratoma with malignant transformation	
• Sinonasal yolk sac tumor (endodermal sinus tumor)	
• Sinonasal teratocarcinosarcoma	
• Mature teratoma	
• Dermoid cyst	

Table 1. Classification of nasal and paranasal sinus tumors (modified by the World Health Organization histological classification of nasal and paranasal sinus cancer) [23].

study by Takahashi et al., sinonasal squamous cell cancer (SCC) is associated with increase in number of EGFR and HER2 copies in about 40 and 20% of the cases, respectively, with their occurrence being mutually exclusive. Expression of these biomarkers is seen in 82% of the cases, usually indicating a worse outcome [20].

There is increasing evidence that the human papillomavirus (HPV) is associated with a subset of sinonasal carcinomas. HPV has been detected in about 30% of sinonasal carcinomas [21]. HPV 16 seems to be the most frequent HPV type. The identification of HPV in sinonasal carcinomas has important clinical implications, because the presence of HPV could be a prognostic factor associated with a favorable outcome [21].

4.3. Pathological classification

The most-common subtypes of epithelial tumor are sinonasal squamous cell carcinoma, which predominantly occur in the maxillary sinus and nasal cavity, and intestinal-type adenocarcinoma (ITAC), which almost exclusively arise in the ethmoid sinus (**Table 1**) [22].

5. Pattern of spread

The pattern of spread of maxillary sinus cancers varies with the site of origin. Suprastructure tumors extend into the nasal cavity, ethmoid cells, orbit, pterygopalatine fossa, infratemporal fossa, and base of skull. Infrastructure tumors often infiltrate the palate, alveolar process, gingivobuccal sulcus, soft tissue of the cheek, nasal cavity, masseter muscle, pterygopalatine space, and pterygoid fossa [24].

Lymphatic drainage from the nasal cavity and paranasal sinus occurs in two directions, anterior, and posterior [25]. The anterior mucosal and vestibular skin drainage is by way of lymphatic channels traveling to the facial, parotid, or submandibular groups of nodes, then to the superior deep cervical nodal chain, primarily level II. The posterior lymphatics course posteriorly to a plexus anterior to the torus tubarius, posterior to the retropharyngeal nodes, and inferiorly to the posterior and superior deep cervical nodes [26]. Studies have demonstrated that SCC is associated with a high incidence of nodal metastasis, neck failure and inferior disease-specific survival rate [27, 28].

6. Clinical presentation

The majority of maxillary sinus tumors present with nasal fullness, stuffiness, obstruction, epistaxis, rhinorrhea, pain, paresthesia to tooth mobility, tooth loss, proptosis, diplopia, and lacrimation [29].

Owing to the nonspecific and the often relatively mild nature of the symptoms at early stages of disease, sinonasal malignancies have a prolonged diagnostic latency [29].

7. Diagnostic evaluation

Inspection and palpation of the orbits, nasal and oral cavities, and nasopharynx can provide preliminary determination of tumor extent. Bimanual palpation is important in assessing contiguous extension of nasal vestibule lesions and in identifying buccinator and submandibular nodal involvement.

For a suspected sinonasal expansile mass, the clinical examination is incomplete without a nasal endoscopy by flexible and/or rigid endoscopes. Nasal endoscopy allows direct visualization of the lesion and may help in differentiating an inflammatory polyp from a neoplasm, benign or malignant. A unilateral expansile mass with an irregular surface, necrotic areas, and contact bleeding ought to be considered as suspicious and potentially suggestive of malignancy.

Endoscopic evaluation may also allow, especially in those cases not completely filling the nasal fossa, identification or suggestion of the possible site of origin of the lesion, its local extension and to assess the presence of satellite lesions. Oral cavity should also be examined to check for loosening of teeth to rule out involvement of alveolar process of maxilla in cases of maxillary sinus malignancy or any oro-nasal/oro-antral fistula; maxillary sinus tumours may also present as a submucosal swelling at level of the cheek, gingiva-buccal sulcus. A recent history of an otherwise unexplainable tooth extraction or mobility should also be considered.

Although the incidence of cervical lymph node involvement is relatively low in sinonasal malignancies, but all cervical lymph node stations must be palpated. The lesions involving the oral mucosa and/or with aggressive histologic behaviour show high risk of lymphatic spreading (i.e., sinonasal undifferentiated carcinoma, high-grade olfactory neuroblastoma). In these cases, clinical evaluation of the neck must be completed by ultrasound so as confirm any neck swelling and metastasis to neck nodes must be confirmed by fine needle aspiration cytology.

Clinical examination of cranial nerves (from I to VI) should be also performed. Malignancies of ethmoid sinus or maxillary sinus can present with alteration of eyeball positioning due to orbital invasion, which can present with proptosis with or without diplopia, due to orbit compression, intraorbital extension or extrinsic muscle involvement. The infraorbital nerve (branch of the maxillary division of the trigeminal nerve) can also be affected especially in lesions extending into the pterygopalatine fossa and/or masticatory space, resulting in sensory disturbances of the cheek. Involvement of cavernous sinus or orbital apex can lead to visual disturbances due to optic nerve infiltration.

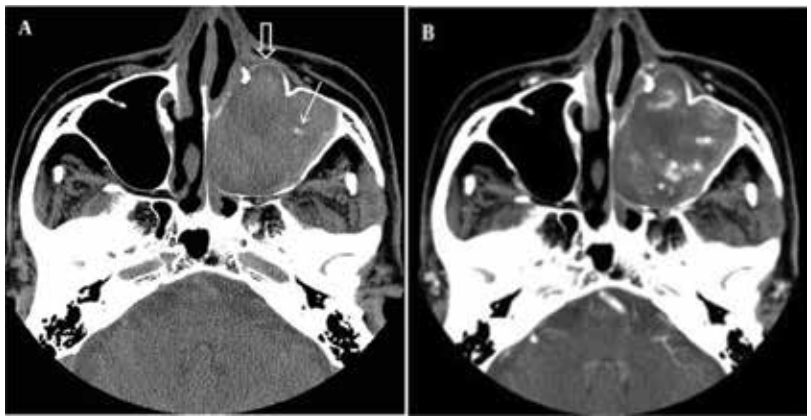

Figure 2. (A) Nonenhanced axial CT scan shows a large, soft tissue mass in the nasal cavity and maxillary sinus, on the left side. (B) Enhanced axial CT of the lesion shows an inhomogeneously enhancing soft tissue mass.

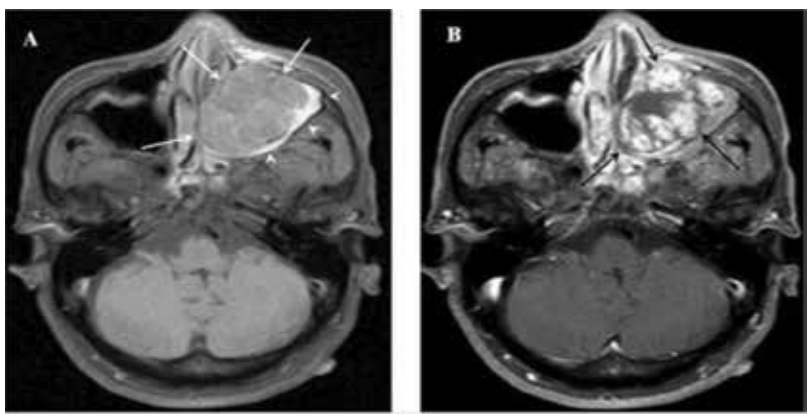

Figure 3. (A) Axial scan shows T1-weighted image with intermediate signal intensity lobulated mass lesion (white arrows) in the left maxillary sinus. Obstructed left maxillary sinus have high signal intensity sinonasal secretions (arrowheads). (B) Enhanced T1-weighted image shows heterogeneous intense enhancement (black arrows).

In the diagnosis of paranasal sinuses tumors MR imaging is a vital tool in the diagnosis of these lesions and is used in conjunction with computed tomography to precisely delineate the extent of neoplasms and involvement of the skull base, the orbits (**Figures 2** and **3**) [30]. The involvement of fine bone structures is best evaluated with contrast-enhanced computed tomography (**CECT**). CECT provides excellent details about the thin bony paranasal sinuses walls separating the ethmoid from the anterior skull base and the orbit [31].

7.1. Biopsy

Transnasal biopsy is preferred for tumors arising from or extending into the nasal cavity or nasopharynx. Some paranasal sinus tumors may be more easily sampled using transoral procedures or an open Caldwell-Luc approach.

8. Staging

The American Joint Committee on Cancer (AJCC) staging system for the nasal cavity and paranasal sinuses (8th edition, 2017) is depicted in **Tables 2–8** [32] (mucosal melanoma of the nasal cavity and paranasal sinuses are not included).

T category	T criteria for maxillary sinus
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues. Floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

Table 2. T staging for maxillary sinus.

T category	T criteria for ethmoid sinus and nasal cavity
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus

Table 3. T staging for ethmoid sinus and nasal cavity.

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)

N category	N criteria
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastasis in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) with clinically overt ENE (ENEC)

Table 4. Clinical regional lymph nodes.

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral or contralateral node 3 cm or less in greatest dimension and ENE(+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

Table 5. Pathological regional lymph nodes.

M category	M criteria
M0	No distant metastasis (no pathologic MO; use clinical M to complete stage group)
M1	Distant metastasis

Table 6. Distant metastasis.

Stage 0	Tis	N0	Mo
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	Mo
	T1–3	N1	M0
Stage IVA	T4a	N0–2	M0
	T1–3	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Table 7. Anatomic stage/prognostic groups.

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Table 8. Histologic grade (G).

9. Prognostic factors

Patient-specific factors (primarily prognostic for survival) include age and performance status. Disease specific factors (primarily prognostic for locoregional control) include location, histology, and locoregional extent (reflected in TNM stage), and perineural invasion. Independent of the treatment type used, the prognosis of patients with sinonasal carcinomas is poor, with an overall 5-year survival rate of 30–50% [33].The 5-year survival rates depend on disease stage and drops from 80% in patients with T1 disease to 30% in patients with T4 tumors [34]. Extensive local disease involving the nasopharynx, base of skull, or cavernous sinuses markedly increases surgical morbidity as well as increases local recurrence often within 2 years of follow up [35].

10. Treatment option overview

Treatment should be individualized based on location and extent of disease, patient performance status, stage of tumor, histopathologic subtype of tumor and availability of local

expertise; because of the rarity of these tumors, consideration should be given to referring patients to centers with experience in their management.

Studies have shown that surgery gives the best results. Early infrastructure lesions may be cured by surgery alone, but, for most other cases, RT is given postoperatively even if margins are negative. Adjuvant Chemo-radiotherapy should be considered for a positive margin. The extension of cancer to the skull base, nasopharynx, or sphenoid sinus contraindicates excision [29, 30, 36].

10.1. Surgery

Surgery can produce excellent control rates for T1 and T2 tumors and is generally the mainstay of treatment.

However for T2 tumors, radiation therapy along with surgery is recommended. In patients undergoing radical surgery, it not only removes the bulk of the tumor but also re-establishes the drainage of involved sinus. It can be further followed by postoperative radiotherapy depending upon the stage of the tumor. Radical neck dissection or elective neck radiation therapy is prescribed only for the patients presenting with positive neck nodes. The incidence of lymph node metastases is generally low (approximately 20% of all cases).

Intracranial extension of tumor (i.e., anterior cranial fossa in cases of involvement of cribriform plate in ethmoid sinus tumors), cavernous sinus, or the pterygoid process; infiltration of the mucous membranes of the nasopharynx; or nonresectable lymph node metastases are relative contraindications to surgery [26, 27].

Maxillary sinus and ethmoid sinus tumors often present as locally advanced disease (large T3 or T4) and are commonly managed with surgery and postoperative radiation therapy. Ethmoid sinus carcinomas can be treated with radiation alone or with concurrent chemotherapy to avoid structural or functional deficits [37].

Surgical approaches include fenestration with removal of the bulk tumor, which is usually followed by radiation therapy or block resection of the upper jaw. Surgery generally involves medial maxillectomy and en bloc ethmoidectomy. A craniofacial approach is required if tumor extends superiorly to the ethmoid roof or olfactory region. A combined craniofacial approach, including resection of the floor of the anterior cranial fossa is used with success in selected patients [38].

Surgical exploration may be required to determine operability. Destruction of the base of skull (i.e., anterior cranial fossa), cavernous sinus, or the pterygoid process; infiltration of the mucous membranes of the nasopharynx; or nonresectable lymph node metastases are relative contraindications to surgery.

10.2. Chemotherapy

Few studies have investigated the role of neoadjuvant chemotherapy in the management of advanced cancer of the PNS [39, 40]. Intra-arterial cisplatin in combination with intravenous paclitaxel and ifosfamide in patients with locally advanced carcinoma of the PNS was studied

at MD Anderson Cancer Center to determine the efficacy, organ-preservation rate, and safety. Despite better organ preservation rates, generous toxicity was also reported [41]. Further study of the role of neoadjuvant chemotherapy in patients with SCC of the PNS is warranted to determine whether the response (or lack of same) to neoadjuvant chemotherapy can help in the choice of definitive treatment [42].

Concurrent chemo-radiation therapy can also be used for patients with medical conditions that preclude surgery if those patients have good performance status. Depending on the patient's performance status and renal function, single-agent cisplatin or carboplatin can be used concurrently with external beam radiation for locally advanced, unresectable squamous cell carcinoma [43].

10.3. Radiation therapy

RT treatment planning includes the entire maxilla, the adjacent nasal cavity, the ethmoid sinus, the nasopharynx, and the pterygopalatine fossa. All or part of the orbit is included in patients with extension into or near the orbit. Target volume definition is aided by the use of treatment planning CT combined with image-fusion MRI.

When using conventional definitive fractionation, the primary tumor and involved lymph nodes (i.e., high-risk sites) generally require a total of 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction) [44]. When using hyperfractionation, high-risk sites generally require up to 81.6 Gy (1.2 Gy/fraction) [45]. In contrast, elective irradiation to low-risk and intermediate-risk sites requires 44 Gy (2.0 Gy/fraction) to 63 Gy (1.6–1.8 Gy/fraction), depending on the estimated level of tumor burden, and on whether 3-D conformal RT or IMRT is used.

For 3-D conformal RT and sequentially planned IMRT, suggest 44–50 Gy (2.0 Gy/fraction). For concurrent chemoradiation the dose is typically 70–70.2 Gy (1.8–2.0 Gy/fraction) in 5 fractions. Higher doses of postoperative RT alone (60–66 Gy), or with systemic therapy, are recommended for the high-risk features of extracapsular disease and/or positive margins (**Table 9**) [46].

Postoperative RT	• T3-T4 primary disease • Microscopic margins < 5 mm (irrespective of intra-operative revision or additional postresection sampling of the surgical site) • >1 additional features at primary: **1.** High-grade disease **2.** Peri-neural invasion (PNI) **3.** Lymph-vascular invasion (LVSI) • Lymph node involvement at pathology **1.** ≥2 lymph nodes **2.** Any lymph node > 3 cm (N2+) **3.** Level IV-V LN positive **4.** Extracapsular extension (ECE)
Preoperative RT	• Locally advanced cancer for downstaging of disease
Concurrent chemoradiotherapy	• Positive (inked) margin • Extracapsular extension

Table 9. Indications of radiation therapy.

10.3.1. Simulation and daily localization

The patient is simulated in supine position with head extended and the head and neck are immobilized. If possible, shoulders should also be immobilized to ensure accurate patient setup on a daily basis especially when an extended-field IMRT plan is used. To spare the tongue from high dose nasopharyngeal region, a bite block can be used.

CT scan with IV contrast using 3 mm thickness should be performed from the top of the head including the brain to the carina. 5 mm thickness can be reconstructed below the clavicle to the level of the carina.

Image registration and fusion applications with MRI and PET scans should be used to help in the delineation of target volumes, especially for regions of interest encompassing the gross tumor, skull base, brainstem, and optic chiasm.

10.4. Complication of treatment

Complications of surgery include failure of the split thickness skin graft to heal, trismus, CSF leak, meningities, parasinusities and hemorrhage.

The most frequent and significant complications of RT involve the eye [47, 48]. When only a portion of the ipsilateral eye is irradiated (the medial one third), it is possible to preserve vision in the majority of patients. When there is extensive disease in the orbit, however, the entire eye is irradiated to a high dose with almost certain loss of vision. A few patients will experience a transient CNS syndrome that includes vertigo, headaches, decreased cerebration, and lethargy [49]. Other rare complications are aseptic meningitis, chronic sinusitis, or serous otitis media.

11. Results of treatment

The management of PNS cancers remains a major challenge in oncology. A major problem in patients with carcinomas of the PNS is that most tumors are highly advanced at the time point of diagnosis.

For single-modality therapies, outcome is generally poor. Amendola et al. compared surgery versus definitive radiation on 39 patients and found no statistically significant differences in survival at 3 and 5 years, with a 5 year survival rate of 31 and 35% for resection and RT, respectively. Later, combined modality treatment was considered superior [50]. A number of reports have demonstrated some improvement in outcome with combined modality therapy. A report by St. Pierre and Baker based on treatment responses of 61 patients treated with surgical resection alone, definitive RT or combined treatment, showed a clear benefit for patients receiving combined surgery [51].

Clinical outcomes of postop patients with carcinomas of the paranasal sinuses and nasal cavity according to decade of radiation treatment were compared at Memorial Sloan-Kettering Cancer Center. In this study, 46% patients were treated by conventional radiotherapy; 35% patients by three-dimensional conformal radiotherapy; and 18% patients by intensity-modulated

radiotherapy. The 5-year overall survival rates were 52%, local control rate was 62%, and disease-free survival was 54%, respectively. There were no significant differences in any of these parameters with respect to radiotherapy technique. The 5-year overall survival rate for patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s was 46, 56, 51, 53, and 49%, respectively. The observed incidence of severe late toxicity was 53, 45, 39, 28, and 16% among patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s, respectively [52].

In the past, the main concern in the radiotherapeutic treatment of PNS tumors was treatment-related toxicity. The introduction of IMRT now allows application of high doses to complex target volumes, while the surrounding OARs can be spared and toxicity may be reduced. Over the last years, IMRT has been implemented widely into the clinical routine. Duthoy et al. compared IMRT with conventional RT in 39 patients with PNS cancers. In the comparison between the IMRT and conventional RT groups, no significant differences were found for LC and OS [53].

Dose conformality to the target volume and conformal avoidance of the organs at risk achieved through IMRT may provide better local control and less optic toxicity compared to conventional radiotherapy technique. Image-guided radiation therapy (IGRT) has also been introduced to complement these approaches in ensuring the safe delivery of a highly conformal treatment, by facilitating convenient and frequent imaging of the patient anatomy throughout the treatment course [54].

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Management of paranasal sinus disorders is not only a test of knowledge but it is also an art form. Great progress has been made on endoscopic sinus surgery in recent decades and this technique lets us look into the remote corners of sinuses. However, we still have a lot of challenging issues. The only way to solve these problems is to face them. Based on these concepts, this book incorporates new clinical and research developments as well as future perspectives in the ever-expanding field of rhinology. The book is a comprehensive reference for ENT residents and practicing otolaryngologists who wish to expand their expertise, develop a broader armamentarium of techniques, and successfully manage their patients with sinonasal disorders.

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