

Diseases of the nose and paranasal sinuses in child

Abstract

Diseases of the pediatric nose and nasal sinuses as well as neighboring anatomical structures encompass a variety of pathologies, especially of inflammatory nature. Congenital disease, such as malformations and structural deviations of the nasal septum, as well as systemic metabolic pathologies affecting the nose and sinuses, rarely require medical therapy from an Otolaryngologist.

The immunological function of the mucosa and genetic factors play a role in the development of disease in the pediatric upper airway tract, especially due to the constantly changing anatomy in this growth phase. Disease description of the nose and nasal sinuses due to mid-facial growth must also take developmental age differences (infant, toddler, preschool, and school age) into account. Epidemiological examinations and evidence based studies are often lacking in the pediatric population. The wide range of inflammatory diseases of the nose and paranasal sinuses, such as the acute and chronic rhinosinusitis, the allergic rhinitis, and adenoid disease, play a role in the susceptibility of a child to infection. The susceptibility to infection depends on the pediatric age structure (infant, young child) and has yet to be well defined. The acute rhinosinusitis in children develops after a viral infection of the upper airways, also referred to as the “common cold” in the literature. It usually spontaneously heals within ten days without any medical therapy. Antibiotic therapy is prudent in complicated episodes of ARS. The antibiotic therapy is reserved for children with complications or associated disease, such as bronchial asthma and/or chronic bronchitis. A chronic rhinosinusitis is defined as the inflammatory change in the nasal mucosa and nasal sinus mucosa, in which the corresponding symptoms persist for over 12 weeks. The indication for CT-imaging of the nasal sinuses is reserved for cases of chronic rhinosinusitis that have been successfully treated with medication. A staged therapeutic concept is followed in CRS based on conservative and surgical methods. Nasal sinus surgery is considered nowadays as effective and safe in children. Based on the assumption that adenoids are a reservoir for bacteria, from which recurrent infections of the nose and nasal sinus originate, the adenoidectomy is still defined as a cleansing procedure in rhinosinusitis. 69.3% of the children had benefit from adenoidectomy.

Comorbidities, such as pediatric bronchial asthma, presently play an even more important role in the therapy of rhinosinusitis; therefore, it is often wise to have the support of pediatricians. In western European countries 40% of children presently suffer from allergic rhinitis, in which pronounced nasal obstruction can cause disturbed growth in facial bones. An early therapy with SIT may prevent the development of bronchial asthma and secondary sensitization to other allergens. Therefore, SIT is recommended in treatment of allergic rhinitis whenever, if possible. The assessment of diagnostic tools is for the examiner not often possible due to the lack of evidence. Rhinosurgical approaches are often described in study reports; however, they lack the standard prospective randomized long-term study design required nowadays and can only be evaluated with caution in the literature.

Keywords: nose, paranasal sinuses, childhood, diseases, rhinosinusitis

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1 Growth and development of the nose and paranasal sinuses

1.1 Prenatal development of the nose and nasal sinuses

The creation of the head is the largest stage in the early development of the embryo and consists of neurocranium and viscerocranium. The human face as part of the viscerocranium develops in the fourth to tenth week through the fusion of five tissue extensions (a median forehead process, and two jaw prominences on either side) [1]. In the sixth week starts the development of the olfactory placode as an ectodermal thickening of the median forehead process. This leads to the development of precursors of the nasal openings (so-called nasal pits), and to the development of a medial and lateral nasal prominence on either side. In the seventh week the medial prominences fuse together in the median plane creating the intermaxillary process, from which later the median nasal content and philtrum originate. The jaw prominences also fuse with the medial nasal prominences creating the nasal openings and connect with the lateral nasal ridges creating the lacrimal-nasal groove. The nasal prominences as precursors of the nasal openings deepen and fuse to a Saccus nasalis. After the development of the palate and nasal septum from the maxillary prominences and forehead process, the first cartilage complex as a support framework begins to develop in the seventh week. The ossification begins ultimately in the fifth month. In the third month mucosa permeates into the lateral nasal wall and begins the development of the nasal sinuses, which correspond to lateral protuberances of the nasal cavity [2]. Pneumatisation of such occur at different time periods. Only the ethmoid cell system is developed at the time of birth. Dysfunction of facial development leads to craniofacial dysplasia, such as cleft lip and palate.

1.2 Postnatal development of the nose and nasal sinuses

Knowledge of postnatal development is based increasingly on modern imaging technology. Postnatally the viscerocranium grows faster than the neurocranium changing the pediatric facial profile leading up to the adult face [3]. In addition, further changes in size and form take place based on gender differences [4]. The intensified development of the midfacial area of the nose and maxilla is of special interest for orthodontic and rhinosurgical procedures in children. With this in mind, the cartilaginous septal wall is the dominating growth area [5]. The perichondrium of the septal cartilage is bound on the cranial border with the periosteum of the nasal bone. The lateral cartilages extend over the entire length of the nasal bones and fuse with the cartilaginous attachment of the frontal skull base. The lateral cartilage and the septal wall build together the septodorsal cartil-

age. The perpendicular plate develops from the ossification of the septal cartilage. The vomer bone is built from a thin sheet of bone and the vomer crest from the basal border of the cartilaginous septum [6]. Studies on the growth rate of the nasal septum without the vomer bone have shown that the maximal rate is reached in newborns, then slowing down until stagnating at the age of twenty and above. The size of the cartilaginous part shows a rapid growth with a maximum at the age of two. The further growth of the entire septum is due to the development of the perpendicular plate with continued ossification of septal cartilage and septo-ethmoidal links [7]. At the same time follows the growth of the nasal concha with a maximum during the first five years of life [8].

At the time of birth, the *ethmoid sinuses* are present in 90% of cases [9]. The ethmoidal air cells grow up to the age of seven, and have an average volume of 4.51 ml at the age of fifteen to sixteen. Orbital complications under the age of six, therefore, usually have their origin in the ethmoid sinuses.

The *maxillary sinus* is also at birth paired like the ethmoid sinuses. At the age of two the maxillary sinus has a volume of 2 ml. Up to the age of nine a volume of 10 ml has been reported. At the age of fifteen the growth of the maxillary sinus, with a volume of approximately 14.8 ml, has reached an end [10]. The largest growth tendency is after the age of twelve when the alveolar crest has been reached. The floor of the maxillary sinus in adults is 4.5 mm deeper than the floor of the nasal cavity. The anatomic relationship of dentition to the maxillary sinus changes over the course of development. Odontogenic maxillary sinus infection with orbital complication is, therefore, more often caused by permanent teeth rather than deciduous teeth.

The *frontal sinus* can be identified at birth and is separate from the ethmoid sinus; however, it starts to expand after birth up to the age of one. After the age of four the frontal sinus starts to pneumatize, and after the age of six 20–30% of children have a radiographic pneumatized frontal sinus. As a child (from birth up to the age of twelve) there is a growth spurt, so that at the age of twelve 85% of children have a pneumatized frontal sinus. Bone resorption, up to the age of 25, leads to the final size of the nasal sinuses [10].

The *sphenoid sinus* is at birth present as a protuberance of the sphenoidal recess. At the age of seven the sphenoid sinus starts growing in a dorsal direction reaching the sella turcica and goes into a growth spurt that ends at the age of fifteen [10].

2 Characteristics of surgical anatomy of the nose and the paranasal sinuses in children

An operation in a pediatric nose can be an elective procedure or directly following a trauma. Unfortunately, the clinical evidence for the effects of such rhinosurgery are

not sufficient. There are many aspects to keep in mind when performing rhinosurgical procedures in children.

One must not only take into account the narrow anatomical conditions, but also the position of the skull base, especially that of the anterior ethmoids which shift during growth in relation to the orbital lamina. The anterior border of the perpendicular plate slides in a caudal direction during growth and can not be used as a landmark during surgery to approximate the location of the anterior skull base [11]. In addition, the poor healing of cartilage, which is essential for midfacial growth, plays an important role. Negative effects of septoplasty in children were already described in 1916 by Hayton. Even today care is warranted in the handling of nasal abnormalities. Animal studies on rabbits have shown that the dissection of the mucosa off the cartilage does not have an influence on the growth of the septum and nose; however, resection of parts of the nasal wall affect midfacial growth – depending on the extent of removal and resulting defect [12]. A larger interruption of the anterior-posterior continuity causes a shortening of the maxilla and nasal bones, a smaller defect usually does not effect the growth length.

The limited healing capacity of the septal cartilage is presently the limiting factor for the effectiveness of surgical procedures and should be accounted for accordingly. The submucosal reimplantation of crashed as well as non-crashed cartilage in the reconstruction of septal defects neither re-establishes the normal growth pattern of the cartilaginous septum, nor its effects to the growth of the midface [11]. Therefore, the aim of all rhinosurgical procedures in children must be to sustain the normal growth of the nasal skeleton by respecting and preserving the anatomical structures.

The age limit for a functional aesthetic rhinoplasty in children has dramatically changed over the past few decades. Mouth breathing with no-exertion is nowadays a surgical indication in children, since an operation at a later point in time for a traumatically dislocated septum would have a serious effect on the development of the nose and midface [13]. Children with obligatory mouth breathing, due to nasal septum deviation, have in comparison to children with normal nasal breathing facial and dental abnormalities [14]. Some authors actually prefer a septoplasty in young childhood and see no negative consequence later in adulthood [15]. Nevertheless, it seems that a consensus in the scientific literature on the effects of rhinosurgical procedures in midfacial development in children is still lacking. The following is certain for the optimal timing for an operation on the pediatric nose: a procedure performed earlier increases the risk in septal development; and a later procedure increases the detrimental effect on midfacial development and mouth breathing [16]. It often seems acceptable to follow a “wait and see” tactic until puberty is reached (Figure 1). Patient consent should not only include clarification of the surgical operation, but also include information on the importance of medical supervision of the facial development up to the end of puberty. A proper photo documentation is extremely important.

3 Congenital diseases of the nose and paranasal sinuses

Deformities of the nose are multifaceted. Deformities in shape are depicted in e.g. the bifid nose with a mild to more severe median split of the nose, or the double nose (also known as proboscis) with a complete second formation. Cleft lip and palate also belong to the clefting congenital deformities, which can during growth influence the form of the nasal alar and later require a surgical correction. The therapy of such deformities is surgical and can be undertaken before school enrollment. Exceptions are the correction of double-sided cleft lip or cosmetically very complex findings. In such cases, a delay till after the maximal nasal growth phase (after the age of twelve) is wise. Deformities of the nasal sinuses are more rare and hardly have a clinical significance. Worthy of mention are the hypoplasia and aplasia cases, in which mostly the frontal sinus in 3–5% of all newborns is absent. Further worthy of mention, although based only on case reports, is the fact that illnesses of the nose and nasal sinuses can also begin prenatally and so must be classified as congenital. Among other things, rising sex hormone levels and an increased sensitivity to allergens that effect the nasal mucosa can trigger rhinitis and epistaxis [17]. The most common deformities will be described in the following text.

3.1 Atresia of the nostrils and nasal atresia

Nasal atresia can be congenital or be due to trauma and severe infection. The congenital atresias are inhibition deformities and result from persistent epithelial dividing membranes, which are usually absorbed in the second trimester of the fetal period [18]. Their occurrence is extremely rare. In the area of the nostrils such congenital atresias are very rare. In addition to the closure of the nasal entrance, the nasal opening to the lacrimal duct can also be occluded. A clue to this can be a dot of pus or an eczema due to the epiphora in the medial corner of the eye. The surgical therapy is in the recanalisation of the nasal entrance and follows the same criteria as the acquired stenosis of the nasal entrance. If possible, therapy should be delayed till after completion of nasal development.

3.2 Nasal fistula

As with the cleft lip and palate, nasal fistulas as well as the intranasal and extranasal meningoceles belong to the group of non-closed fissures. Median nasal fistulas are with an incidence of 1:30,000 very rare deformities. They are usually isolated cases not associated with syndromes or other deformities. The median nasal fistula is considered a remainder of the median nasal cleft. The external opening of the subcutaneous fistula lies in the middle of the nasal dorsum. The end of which lies in the

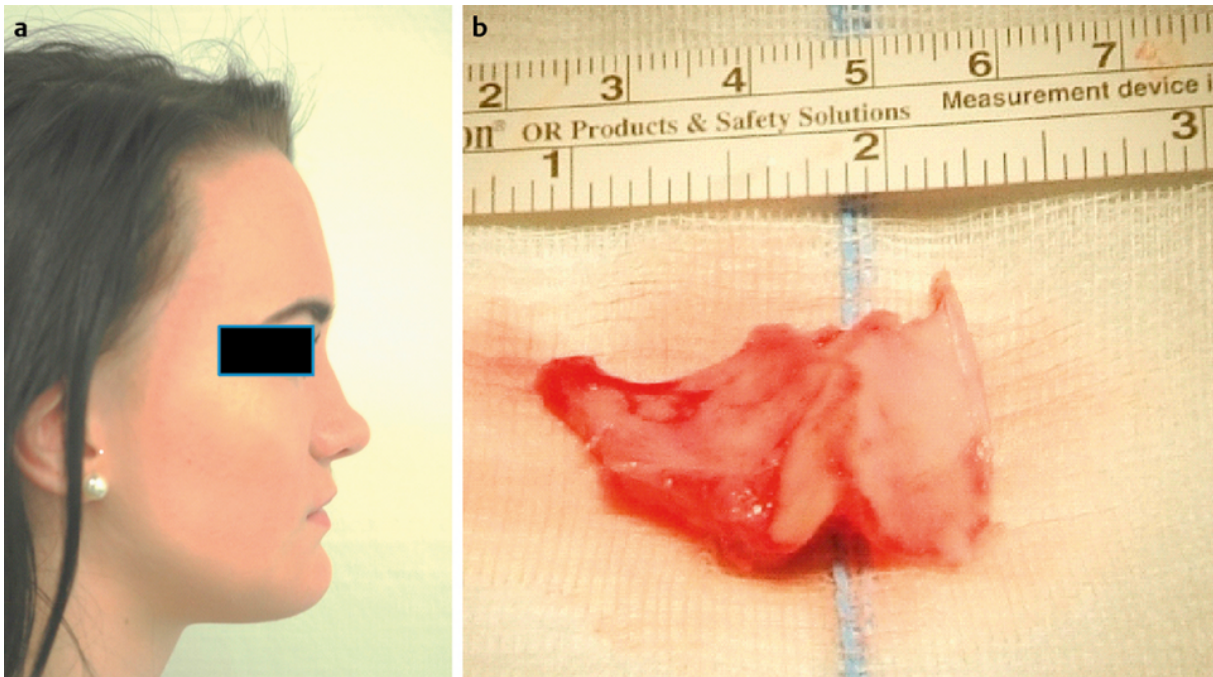


Figure 1: a) 18-year-old female patient after nasal trauma in childhood at the age of five. b) Intraoperative finding of the cartilagenous septum with severe irregularities.

area of the glabella; however, it can also extend to beneath the nasal bone. Fluid can collect in the duct fistula creating a nasal cyst. Due to the fact that the duct is covered with squamous epithelium, there is a tendency for inflammation. In rare cases a septal abscess can develop [19]. The therapy of choice is the complete extirpation, in which plastic-reconstructive measures can be done simultaneously or at a later time. The surgical removal poses difficulties only when the fistula continues beneath the nasal bone.

3.3 Meningoencephaloceles

Nasal Meningoencephaloceles develop due to failure of the anterior neuropore to close in the third gestational week. One differentiates between the outer extranasal celes from the internal, intranasal (basal) celes. Extranasal celes appear as a distension in the root of the nose. Intranasal celes can be seen hanging in the nasal cavity and appear as nasal polyps [20]. This can lead to a misdiagnosis and a nasal polyp removal operation, which can lead to serious complications (e.g. liquorrhea, meningitis). Even without a preceding operation "spontaneous liquorrhea" can actually happen spontaneously [21]. Furthermore, the dura in the intranasal celes can cause the septum to seem inflated. The differential diagnosis would then be a septal hematoma or septal deviation. The frequency of nasal meningoencephaloceles corresponds to about one per 3,000–5,000 births. Since recurrent meningitis can often occur, it is recommended to resect the cele with a reconstructive duraplasty through a rhinological and/or neurosurgical approach [22].

3.4 Choanal atresia

The most common deformity of the nose interiorly is the congenital choanal stenosis or complete atresia. The incidence of this deformity is one per 8.000 births. It can be single-sided or bilateral, membranous or ossified. The single-sided deformity as well as the occurrence in females is five times for common. Due to a horizontal extension of the palatal process around the eighth gestational week, the oral cavity is separated from the nasal cavity and the primitive choanae are sealed. At this point there is a membrane behind the nasal cavity, which separates the nasal cavity from the epipharynx. Only after the absorption of this membrane does the secondary and definitive choana develop [22].

The single-sided deformity can be endured for many years as long as the air supply of the other side is adequate, and is often recognized at a later time. A cardinal symptom is the single-sided discharge due to the blocked transport of secretions to the nasopharynx. If one occludes the other side, any form of breathing is not possible on the affected side. The identification of the atresia is done with the politzer balloon, exploration with fine catheters, or radiographic contrast imaging in the supine position. In children the differential diagnosis is mainly the exclusion of a foreign body. The surgical correction of the atresia plate should not be undertaken before school age, it should rather be done after the age of ten [23].

The bilateral choanal atresia behaves in a completely different manner. There must be an immediate surgical therapy. Due to the higher position of the larynx of a child, in comparison to that of an adult, it is possible for a small child to breathe at the same time as eating. This helps

reduce the risk of an aspiration pneumonia until the reflex pattern of swallowing has been properly learned. As a consequence of this, newborns can not breathe through their mouth. The bilateral choanal atresia then leads to a life threatening condition. The diagnosis of the bilateral choanal atresia is relatively simple to make with the aid of a soft plastic catheter, which is placed in the nose and advanced into the pharynx. If breathing through the nose is not possible, then suckling is also not possible. This requires feeding through a stomach tube initially. After the first few weeks it can be expected that the infant has adjusted to breathing through the mouth. The most common surgical approach is the transnasal puncture of the closure and the safeguarding of the new opening with a plastic tube, which is fixated on the septum [24]. The opening of an ossified stenosis can also be performed with a drill transnasally. If the opening is not splinted, a closure will again occur. As the child grows the catheter has to be changed and the size adapted. There are many other surgical methods in addition to the transnasal endoscopic method; however, none has been shown to be superior to the other [25].

3.5 Deformities of the nasal septum

Studies on human fetuses have shown that 25% of fetuses at five months have a deformity of the posterior septum. The most common localization was the interconnecting area of the cartilaginous septum with the vomer and perpendicular plate. This percentage increased to 37% by the time of birth [26]. Teul et al. performed computed tomography imaging on 105 miscarried fetuses in the 12th to 40th week and found 14% of cases with a septal deviation of 34% from the vertical axis [27]. A severe obstruction of nasal breathing due to a septal deviation or external deformity is an indication for surgical correction (Figure 1). Recommendations against opened approaches are currently not known. It is often preferred to postpone the operation till after growth development, since the established methods of septorhinoplasty in adults do not necessarily apply to children.

4 Physiology of the nose and paranasal sinuses in the pediatric development

As is typical in the adult, the function of the pediatric nose is the humidification, warming, and filtering of the air we breathe, as well as to defend against germs. The human airways go through an important change in infancy and preschool age with significant adjustments in airflow. Especially the airflow ratio of oral to nasal breathing decreases with increasing age. The nasal respiratory volume increases from 6.4% in a ten-day old infant to 40.3% in a five year old child when compared to an adult [28]. Children are used to nasal breathing; therefore, nasal packing should not be used. The inspired air is controlled

by the olfactory organ located above the roof of the nose. The sense of smell matures with age and the function correlates with the growth of the olfactory bulb [29]. Specific nasal reflexes serve to protect the respiratory system as well as regulate the air. The nasal cavity serves as a resonating cavity and for the generation of consonants to assist in phonation [30]. The function of the nasal sinuses is still an ongoing research topic.

The *nasal mucosa* is the first point of contact of the body with inspired antigens and pathogens; therefore, crucial for the immune defense. The nasal epithelium is built up of ciliated columnar epithelium. Basal cells over a basal lamina, differentiate into intermediary cells that in turn differentiate into epithelial cells on the epithelium surface. The upper epithelial layer consists mainly (up to 70%) of nonciliated and up to 20–50% of ciliated epithelial cells, as well as 5–15% of goblet cells (Figure 2). A 10–15 µm thick mucus layer covers the ciliated cells and fills the gaps in between the cilia. The ciliated cells are responsible for the mucociliary clearance, in which the transport of secretion is directed toward the choana.

The surface epithelium in the nose has one of the most important immunological functions of the nasal mucosa: the *barrier function*. The barrier function of the epithelium is due to proteins, so called tight junctions that are located in the apical area of the lateral cell membrane. They are organized in dense protein bands that establish a tight contact between the cells. On the one hand, the tight junctions ensure a diffusion barrier to the paracellular space above the epithelium (=non-permeability of tissue). On the other hand, they regulate the free transport of membrane components with the preservation of cell polarity and the directional material transport (Figure 2) [31], [32]. In addition to the barrier function, the nasal and paranasal sinus mucosa plays an important role in the immune defense. A considerable portion of the immunity is due to the synthesis of antibody immunoglobulins (Ig)-A and IgG in plasma cells (B-lymphocytes) of the nasal mucosa [33]. Antibodies of IgG and IgA isotype are extremely cytotoxic and kill microorganisms on the mucosa surface. The killing of pathogens activates a network, the so called mucosa associated lymphoid tissue (MALT), which is linked with the systemic immune system [34], [35].

In humans it is assumed that the lymphatic tissue under the term “Waldeyer’s ring” is equivalent to MALT or GALT (gut associated lymphoid tissue), and NALT (*nasal associated lymphoid tissue*) [36]. It is currently not known if NALT exists in primates. In a post mortem examination in children under two years of age that died from sudden infant death syndrome, it was shown that organized lymphatic tissue appeared in the area of the nasal concha that was structurally similar to peyer’s patches [37], [38]. The development of immune tolerance and the IgA dependant secretory immunity strongly fluctuate after birth in all bordering surfaces of the nose, bronchi, and intestine. A disturbed barrier function of the epithelium with increased permeability is the basis for the pathogenesis of many illnesses in the nasal mucosa, such as allergies

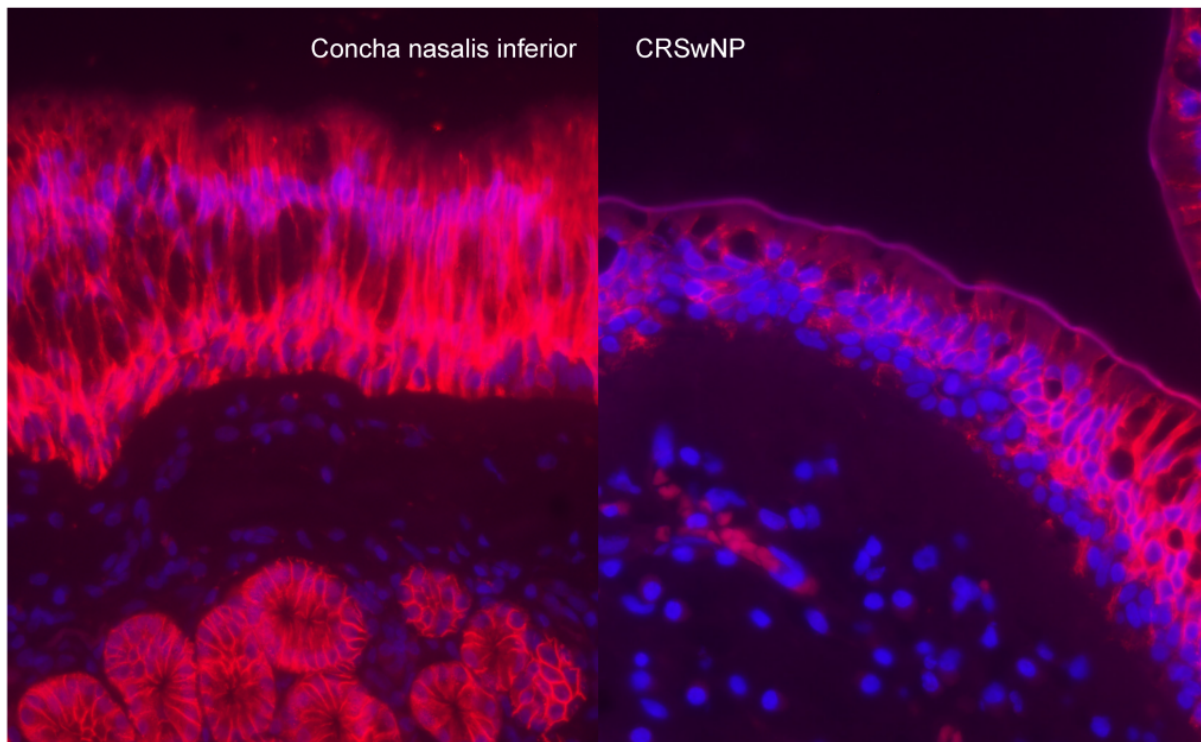


Figure 2: Immunofluorescence analysis for the tight junction protein claudin 7 on a histologic section of a healthy patient (left) and an eleven-year-old child with polyposis nasi (right)

and recurrent infections with microorganisms. The barrier function is dependant on the age of the patient, genetics; and the immunological network of cells, nerves and neuropeptides, and inflammatory substances. Many studies have shown that allergies begin with a late and deficient development of the IgA system [39].

Expression of SIgA in nasal secretion of healthy child varies in circadian pattern, SIgA mean value in healthy children is lower than those values measured in 10 healthy adults. Furthermore, the 24 hours concentration profile of SIgA is more stable in healthy adults [40]. The circadian rhythm normally depends on activity in the suprachiasmatic nuclei that orchestrate sleep- wake cycles, cardiovascular activity, endocrinology, body temperature. Nasal cycle and mucociliary transport are also regulated by these processes in brain and vary age dependent. *In childhood there is an insufficient number of ciliate cells and mucus-producing cells so that mucociliary transport becomes insufficient. The periodic waxing and waning in turgidity of nasal mucosa are not alternate but synchronous on both sides in child* [41], [42].

5 Specialities of rhinosurgery

5.1 Pediatric septoplasty and rhinoplasty

Surgery of the nasal septum in a child should be as conservative as possible and as extensive as necessary. The application of polydioxanone (PDS) sheets has been examined in the reconstruction of septal defects in adult rabbits [43]. It seemed that the PDS-sheets stimulated

cartilage growth. The septal defects were filled with newly developed cartilage within 25 weeks. After the reimplantation of resected pieces of septal cartilage that was sutured to PDS, deviations and duplications were, as expected, observed significantly less. Although there has been much promise in the advances of tissue engineering, the results are not sufficient enough to have a routine implementation in the ENT-field.

The growth spurt of the nose in puberty reaches its maximum for girls at the age of eight to twelve, and for boys at the age of about thirteen. The steepest decline in the growth curve, the end of the nasofacial growth spurt, has been determined as 13.4 years for girls and 14.7 years for adolescent boys [13]. Another study group has concluded, based on a meta-analysis, that a rhinoplasty can be performed without risk after the age of 16 in girls, and after the age of 17 in boys [44]. Vorwoerd et al. summarized in a report in 2010 several essential recommendations to surgical aspects of the developing nose [11]. The most important are listed as follows:

- The mucosa of the nasal floor should not be lifted in order to prevent injury to the incisive nerve.
- Incisions in growth and support areas, especially in the (spheno-) ethmoidodorsal area, should be avoided.
- A posterior chondrotomy or dissection of the septal cartilage off of the perpendicular plate should be avoided, since this could influence the reinforcement and growth of the nasal septal wall.
- The septospinal ligament (connection of the cartilaginous septum with the premaxilla) should not be cut, since this fixates the septum in the midline.

- Postoperative instability of the supportive frame should be avoided by means of repositioning and fixation.
- Intraseptal collection of blood should be avoided.
- Alloplastic and biomaterials should, since lacking in growth capability, be avoided. Autologous cartilage should rather be used when possible.
- Osteotomies do not pose a threat to the developing nose, since bone fractures completely heal. Lastly, the basic principle applies: the more conservative, the better.

5.2 Surgical intervention of the turbinates

Surgical procedures on the inferior turbinates are recommended in children in extreme cases of nasal obstruction caused by secondary turbinate hypertrophy. The indication to a surgical intervention is based on the exclusion of a nasal septum deviation, adenoids, choanal atresia, and foreign bodies. The rhinitis medicamentosa and the stuffy nose syndrome in infants and small children must also be ruled out as a differential diagnosis [45], [46] according to Scheithauer [47]. It is assumed pathophysiologically that the nasal obstruction leads to a disturbed climatisation function of the nose with accompanied infections of the upper airways. It is further hypothesized that a disturbance in facial growth can result from the permanent breathing through the mouth [48].

Surgical approaches for the reduction of nasal turbinates are till now neither for adults, nor for children standardized. There is a lack of evidence based studies, especially in children, for the objective long-term results of different procedures on the reduction of nasal turbinates. Accepted methods for nasal turbinate reduction include *total turbinectomy, the inferior turbinoplasty, the submucous turbinoplasty, turbinate reduction by use of CO₂ and YAG lasers* [47].

The magnitude of surgical intervention in children in nasal turbinate surgery is controversially discussed. Principally, the mild reduction of turbinate tissue is recommended in order to prevent postoperative growth defects as would be the case in radical septoplasty [49]. Other authors examined the *partial or total turbinectomy* in children at an age of 9–15 and under 16. The one study reached a success rate of 68% without any occurring complications, such as bleeding, synechia, or smell disorders [50]. The other study reported a success rate of 91%. A scab formation or atrophic rhinitis was not reported postoperatively [51]. A further study showed an improvement in asthmatic discomfort in an observational period of 4–6 years in 27.3% of the children [52]. Another study examined 20 children, younger than ten years of age, that had a total turbinectomy performed; 78.9% of the children were free of symptoms at one year, 14.5% improved in symptoms, and 6.6% had no changes. It came to a disturbance in wound healing in 6.6% of cases [53]. *Even after an observational period of 14 years there was no change in midface development* [51]. The efficacy of turbinoplasty was also examined in a study with

64 children. Weider and Sulzner published a study in 1998 stating a success rate of 89% after 94 months [54]. According to Stoll, a submucous turbinoplasty is indicated when in addition to a mucosal thickening a spongy swelling of the os turbinata is present [49], [55], [56]. Procedures involving lasers in pediatric turbinate surgery are still not well evaluated. In general, due to deeper penetration of the ND-YAG laser, it is not favored in children [57]; the CO₂ laser can be used in the single-spot method in children in general anesthesia as a minimally invasive surgical option [58].

5.3 Surgery of nasal trauma

Due to the gradual ossification of the nose of the newborn, the cartilaginous frame of a child is more susceptible to trauma, and an injury at a young age can have severe consequences later in age. Trauma of the nose in children is quite often. Most injuries of the nasal skeleton are neither diagnosed, nor treated, and can later lead to aesthetic and/or functional problems [13], [59]. It is usually the case that a post-traumatic evaluation of a pediatric nose is difficult due to rapid swelling. This usually makes the re-evaluation necessary in a few days after the use of decongestant measures. In addition to the nose, the orbital rim, palate, and maxilla must be examined. The endonasal conditions should be evaluated with a rhinoscopy. Diagnostic modalities for a child include x-ray imaging and the ultrasound of the nose. Ultrasonic examination can properly visualize cartilaginous dislocations and fractures [60], [61].

5.3.1 Repositioning of fractures of the nasal skeleton

A fracture of the os nasale is the most common midface fracture in children. Due to the fact that the nasal bones are less developed and are still partially cartilaginous, bone fractures are less frequent than in adults. On occasion, an interruption can be seen in the suture on the border of the nasal bones. This can usually be repositioned manually by applying external pressure. Acute nasal skeleton fractures in children are always treated in general anesthesia. The nasal dorsum is elevated, thereby straightening the nasal septum, and at the same time the nasal bones are manually reduced [62]. The elasticity of the septodorsal cartilage as well as its tendency to take on the initial form is of major importance for success. The therapy does not differ from that of an adult [63]. However, since children are used to nasal breathing, nasal packing should not be used.

5.3.2 Injuries to the nasal septum

Fractures in cartilage do not heal well; therefore, cartilage growth after a septal cartilage fracture usually causes a septal deviation [64]. Predisposed fracture points are thin zones predominately in the central part of the perpendicular plate [11]. Due to the more frequent occur-

rence of nasal trauma in childhood in comparison to adult age, it seems plausible that a large proportion of septal deformities in adults are a result of pediatric trauma, most of which are at the time of injury not examined by a pediatrician or otolaryngologist [62]. It is known today that the developing septodorsal cartilage of children is essential for the growth of the midface. Not only the growth of the nose, but also of the maxilla are inhibited by an early childhood septal injury. The long term effects on midfacial development are more evident the younger the child is at the time of injury and when destruction to the nasal septum happens [48].

5.3.3 Septal hematoma and abscess

As is the case in adults, a septal hematoma or abscess requires the immediate surgical intervention in order to prevent a destruction of the cartilage. In addition to the drainage, repositioning of mucosal sheets, and sufficient antibiotic coverage, resected defects should be patched with homologous cartilage in order to prevent a saddle nose deformity [65]. Support of the implanted material with fibrin glue or PDS-sheets is rational. The reconstruction of the septum in the acute setting seems to also have positive long term effects on growth, form, and function of the nose [66].

5.3.4 Hematoma of the nasal dorsum

Fractures of the lateral cartilage with injury to the terminal branch of the anterior ethmoid artery can cause hematoma of the nasal flank. This appears as a bulge in the lateral nasal wall on endoscopic view. The hematoma should be drained in this area. The dislocated lateral cartilage should be pushed onto the nasal bone with internal nasal packing.

6 Inflammatory diseases of the pediatric nose and nasal sinuses

Included in the terminology “inflammatory diseases of the nose and nasal sinuses” are a wide range of diseases, e.g. the viral rhinitis, the acute sinusitis, the common cold, the allergic rhinitis, and the chronic rhinosinusitis, all subsumed and classified. Specific etiologic factors, such as the formal pathogenesis and therapy of inflammatory diseases, are being scrutinized in comparison to adults in a critically evidence-based manner. This is often due to the insufficient understanding of the therapy of inflammatory diseases of the pediatric upper airway. The clinical manifestation of inflammatory diseases of the nose and nasal sinuses varies extensively in children in comparison to adults due to the anatomical conditions, growth, and immunological processes.

6.1 Pediatric rhinosinusitis

Analogous to the definition of rhinosinusitis in adults, the rhinosinusitis in children is defined as an inflammatory illness of the nose and nasal sinuses [67]. Since the mucosa of the nasal sinuses is simultaneously diseased during a rhinitis, the term rhinosinusitis is preferred to sinusitis. The rhinosinusitis is defined based on certain clinical characteristics. Typical rhinosinusitis symptoms include: *midface pressure or pain, nasal secretion, nasal obstruction, hyposmia, and coughing*. In order to make the diagnosis at least two of the three symptoms must be present according to the current guidelines. Usually the nasal obstruction and the nasal secretion, either the anterior or posterior nasal drip, is included. The severity of disease can be determined based on a visual analog scale (VAS) of 0–10 cm graduation: Level – mild = VAS 0–3, Level – intermediate = VAS 3–7, Level – severe = VAS 7–10 [67].

The differentiation between acute rhinosinusitis and chronic rhinosinusitis is based on the time duration of clinical symptoms. An acute rhinosinusitis corresponds to a duration of clinical symptoms of less than 12 weeks, while the chronic sinusitis corresponds to a duration of symptoms of over 12 weeks [68].

6.1.1 Acute rhinosinusitis (ARS)

The acute rhinosinusitis in children develops after a *viral infection of the upper airways, also referred to as the “common cold” in the literature*. It usually spontaneously heals within ten days without any medical therapy. In the European position paper of EPOS, Rhinosinusitis is defined as a sudden onset of two or more of the typical rhinosinusitis symptoms (nasal secretion, nasal obstruction, midface pain or pressure, hyposmia, and coughing) for less than 12 weeks a year [68]. Symptom-free intervals are present between episodes. A postviral rhinosinusitis corresponds to an acute rhinosinusitis – in which the symptoms have intensified after five days of onset, or in which the symptoms persist even after ten days.

The *clinical diagnosis of the acute rhinosinusitis* in children poses a diagnostic challenge because the distinction to symptoms of other inflammatory diseases of the upper respiratory system (e.g. to allergic rhinitis) is often not possible. The symptoms are often subtle and the history limited to observation and subjective assessment of the parents. The endoscopic examination is often not tolerated in young children. Therefore, the diagnosis must be made based on the history, observation, and chronologic findings. It could be shown in studies that purulent rhinorrhea and nasal obstruction suggest the diagnosis of an acute rhinosinusitis [69], [70]. *Typical symptoms of ARS in children include fever (50–60%), rhinorrhea (71–80%), cough (50–80%), and pain (29–33%)* [71]. In a study of 60 children (average age 5.7 years), the impact of the symptoms purulent rhinorrhea, facial pain, and nasal secretion were examined based on morphologic changes seen in MRI examinations. The children had the

relevant symptoms six days before the examination. The results showed that approximately 60% of the children have a pathologic shadow in the sphenoid sinus, and 18% of cases in the frontal sinus. After two weeks, a clinical re-examination showed that 26% of the children had a significant reduction of symptoms [72], [73].

The *acute bacterial rhinosinusitis* arises, according to the current guidelines, when a viral infection of the upper respiratory airways persists for more than ten days, or when after initial symptom improvement - the complaints worsen [68]. In a study of 112 children between the ages of six months and 35 months, 623 infections of the upper airways within a three-year period was observed. In the viral infections 8% became complicated due to a bacterial rhinosinusitis; 29% of these episodes marked an increase in level of symptom severity in the study. In the group of 6–11 month old infants and the group of over 24 month old children the frequency of rhinosinusitis was 7%, in the group of children between 12–23 months of age the frequency was 10% [74]. In another study, the incidence of bacterial rhinosinusitis was determined as 4–7.3% [75]. The incidence of children during the first year of life was set higher. Children under the age of five had on average of two to seven episodes a year.

Included in the *differential diagnosis* is the unilateral secretion of the nose, a foreign body in the nose, or a *unilateral choanal atresia*. The *acute adenoiditis* imitates symptoms of the ARS. The adenoid size usually decreases with ongoing age [76]. Adenoids are largest at the age of four to five. In a study with 287 children and typical ARS symptoms it was attempted to differentiate between adenoiditis and ARS. A nasal endoscopy was performed and the diagnosis was made based on the localization of purulent secretion. Purulent secretion in the ostiomeatal unit and in the ethmoidal area allocated the illness to the ARS group, while purulent secretion on the adenoids confirmed an adenoiditis. Rhinosinusitis was diagnosed in 89.2% of the patients, combined with adenoiditis in 19.2% of cases. An adenoiditis alone was only diagnosed in 7% of cases in the cohort. The combined form of inflammatory disease of the upper airways was more common in younger children at the age of two to five. The isolated rhinosinusitis was more frequent in older children [77]. The most common microorganisms that cause a *bacterial ARS* are *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, and *anaerobes* [78]. Although in the period from 1998 to 2007, the rate of medical consultation in the USA due to middle ear infection considerably dropped, the frequency of medical visits due to ARS remained stable; 11–14 medical visits per 1,000 children has been published in the literature [79].

The diagnostic evaluation includes the physical examination and detailed history taking as well as the *rhinoscopia anterior* to assess the inferior nasal concha, the middle meatus, and the characteristics of the mucosa. The nasal endoscopy is also helpful in examining the adenoids and posterior nasal space; however, this can only be done when the child is at a certain age allowing the examina-

tion. Examination of the posterior wall of the pharynx also sheds light on postnasal secretions or cobblestone-changes to the mucosa.

A swab test is usually not necessary in an uncomplicated acute rhinosinusitis. A swab test is necessary when children do not respond to conventional medical therapy within 48–72 hours, or an immunodeficiency exists [80]. The gold standard in making the diagnosis of bacterial ARS includes the swab test from aspirated secretion out of the maxillary sinus. Unfortunately, this method is too invasive for children. For this reason it is preferred to take a swab test from the middle meatus, since the results correlate well with those taken from the maxillary sinus (according to the literature). Although the diagnosis of ARS in children can be made based on clinical symptoms, the American Academy of Pediatrics published and recommends in their 2001 guidelines the computed tomography as the imaging of choice [81]. *Computed tomographic imaging should, in this context, only be used on patients with persistent symptoms after 10 days of ongoing complaints with evidence of endocranial or orbital complications*. Magnetic resonance imaging of the nasal sinuses, orbita, and endocranium can always be done by suspicion of complications.

Antibiotics are the most common medication used in the therapeutic treatment of ARS. In a meta-analysis of randomized, controlled studies three of 17 reports were evaluated dealing with antibiotic therapy in pediatric acute rhinosinusitis. A total of 3,291 cases (2,115 adults and 306 children) were included in the meta-analysis. The diagnosis of the acute rhinosinusitis was made based on clinical criteria, radiographic or other clinical laboratory test parameters. In most studies, patients were included with a duration of symptoms of at least 7–10 days. The results showed that in comparison to the placebo group, the antibiotic group had a higher rate of healing within 7–15 days. The difference was significant, but not very pronounced [82]. In a further study, amoxicillin combined with clavulanic acid was examined in a group of children between the ages of one to ten with acute bacterial ARS in comparison to a placebo group. A score based on symptoms was made at different time points. The children were all evaluated on day 14 after the onset of therapy and classified as healed, improved, or worsened. Children that received antibiotics seemed to be in the healed category more often (50% versus 14%, $P=0.01$), and were less prone to having a therapy failure (14% versus 68%, $P<0.01$) in comparison to the placebo group. As shown in other studies, there were no side effects in comparison to the placebo group [83], [84]. A further study examined children at the age of 1–15, in which ARS had been diagnosed based on clinical and radiographic findings. The children received cefditoren (8–12 mg/kg per day), a third generation cephalosporine, versus amoxicillin/clavulanic-acid (80–90 mg/kg per day) for 14 days. The results showed similar but not statistically significant differences on day 14 [85].

In summary, the results of the existing studies show that most cases of *uncomplicated ARS heal independent of*

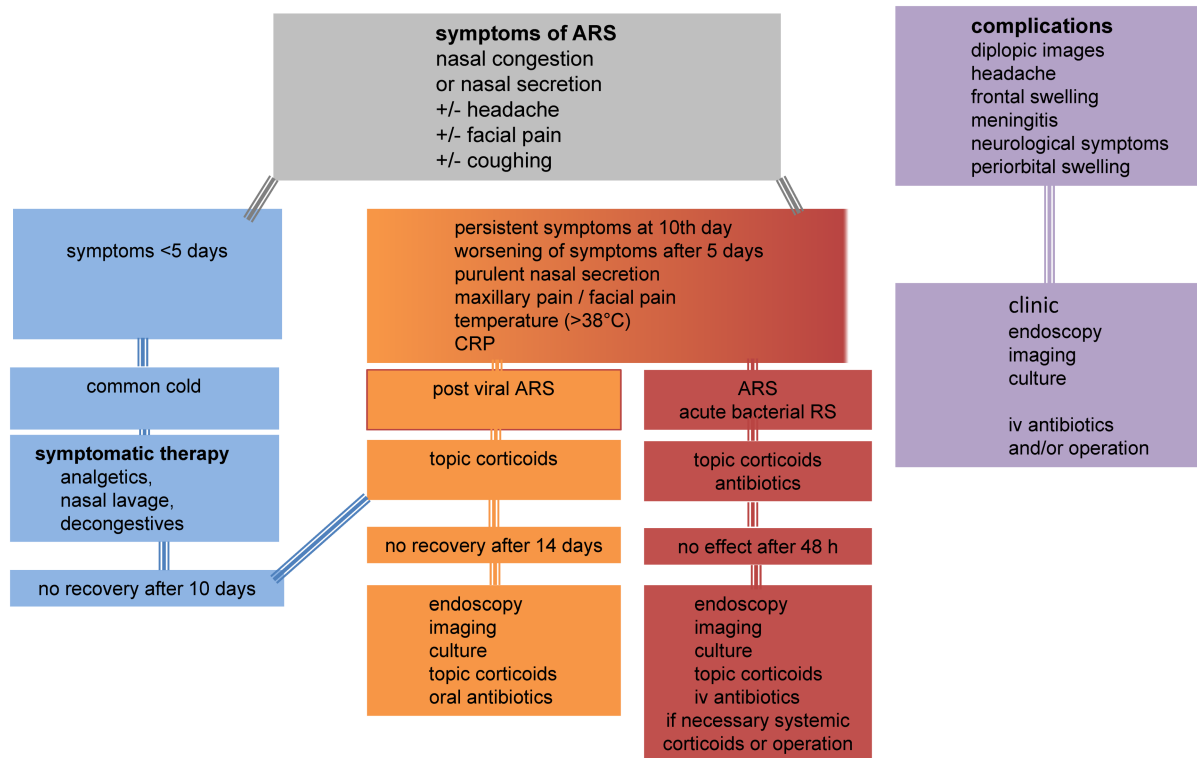


Figure 3: Management of acute rhinosinusitis in childhood modified according to EPOS

therapy. An improvement in symptoms is seen by the use of antibiotics. Based on this fact, it can be inferred that antibiotic therapy is prudent in complicated episodes of ARS. The antibiotic therapy is reserved for children with complications or associated disease, such as bronchial asthma and/or chronic bronchitis (Figure 3). In this context, the data shows that an antibiotic therapy accelerates the therapy of ARS. It must still be examined if antibiotic therapy increases the risk of antibiotic resistance. The therapy recommendation is then amoxicillin 40 mg/kg per day to 80 mg/kg per day. Amoxicillin with clavulanic acid and cephalosporine should be given when β -lactamase producing bacteria are found. In cases of hypersensitivity, the antibiotics trimethoprim, azithromycin, and clarythromycin can be used as substitutes [68].

Efficacy of nasal glucocorticosteroids in the therapy of ARS

The therapy of ARS with nasal steroids is currently considered favorable (evidence based) as a monotherapy in older children [68]. However, studies are limited in pediatric ARS in comparison to adults. Barlan et al. studied 89 children with acute ARS receiving amoxicillin/clavulanic-acid combined with budesonide versus placebo. Significant improvement could be shown in the scores for coughing and nasal secretion at the end of the second week in the therapy group [86]. Other studies with mixed populations, adults and children (usually 12–14 years of age), have shown similar results with the application of intranasal steroids in combination with antibiotics. In another randomized placebo controlled study, patients older than twelve were treated with mometasone versus

placebo or amoxicillin. The symptoms were reduced more in the monotherapy as compared to the control group. There is no evidence for younger children due to the lack of studies [87], [88], [89], [90], [91].

Other forms of therapy for the acute rhinosinusitis

The evidence of supportive therapy (such as the application of oral and nasal antihistamines, nasal douches, and β -adrenergic topical substances) were evaluated in a systematic Cochrane review. Out of 402 articles, 44 publications were included that fulfilled the requirements of a randomized control set-up. Based on these results, it is not possible to determine an evidence based therapy for ARS; therefore, the authors concluded that a supportive therapy does not offer any advantage [92]. In a randomized placebo controlled study published in 2010 from Unuvar et al. the mucolytic substance erdosteine was examined versus placebo on 80 patients with an average age of 8.5 years. Both patient groups showed a vast improvement of the symptoms on day 14, and there was no significant difference between the two groups [93]. A mucolytic therapy is, therefore, not recommended.

6.1.2 Complications of the acute rhinosinusitis

Complications of ARS include orbital, intracranial, and osseous inflammatory changes – as in osteomyelitis. Historically, complications in ARS were witnessed more often in the pre-antibiotic era. Thanks to current diagnostic tools, such as CT and MRI imaging, the extent of complications in ARS are better recognized. Children are predisposed to orbital complications, whereas adults

develop complications due to chronic rhinosinusitis. Orbital complications present in about 60–70% of cases, about double as often as intracranial complications (15–20%). ARS complications that affect the bones in the facial skull area present in 5–10% of cases [94]. Although orbital complications usually appear in younger children, intracranial complications can occur at any age. It could also be shown in studies that a seasonal dependence with formation of complications in the winter months could be proven. In spite of antibiotic therapy, infections of the nasal sinuses can lead to complications when the infection is not completely healed [95]. National epidemiologic studies estimate a complication rate for the acute rhinosinusitis of approximately three episodes per million inhabitants per year [96], [97], [98], [99]. In comparison to adults, the orbital complication in children is often painless [100]. In order to safely make the diagnosis of an orbital complication, an ophthalmological examination is necessary in addition to the clinical findings. Imaging (CT) is recommended in cases of protrusio bulbi, double vision, and a conjunctival edema with chemosis.

6.1.2.1 Orbital complications in the acute rhinosinusitis

The classification of orbital complications is based on Chandler [101]. The method of choice to secure the diagnosis is a low dose CT. Direct coronal slides can be generated by coronal reconstruction using a (multi-slice) spiral CT dataset. Orbital complications are classified according to Chandler as shown in Table 1.

Table 1: Classification of orbital complications (Chandler, 1970 [101])

Preseptal phlegmon (eyelid phlegmon)
Periostitis of the Lamina papyracea, intraorbital phlegmon
Subperiosteal abscess in the orbit
Orbital abscess
Cavernous sinus thrombosis

The preseptal cellulitis (eyelid phlegmon) is from an anatomical standpoint not an intraorbital complication. Since the orbital septum is the anterior border anatomically to the orbit, the description should be that of an eyelid phlegmon rather than a preseptal cellulitis [102], [103]. From a clinical perspective, the preseptal phlegmon is distinguishable from other stages of orbital complication due to the lack of exophthalmus and painful eye movements with double vision [104]. Imaging is often not necessary in such cases. Based on the clinical findings and the rather favorable prognosis in comparison to other stages of orbital complication, the therapy of choice for the eyelid phlegmon is an oral antibiotic [94].

The *periostitis of the lamina papyracea* and *intraorbital phlegmon* are often present as complications of an acute rhinosinusitis [105], [106]. The symptoms in children are characterized by an exophthalmus, a reduced and painful eye movement, and a reduction in vision (red-green color vision). In the differential diagnosis, one should rule out

a subperiosteal abscess through appropriate imaging. The therapy consists of an intravenous antibiotic regimen. An ophthalmological examination should also be performed. A subperiosteal abscess originates through the progression of the infection into the orbit. Pathophysiologically, the infection travels often through a dehiscence lamina papyracea into the orbit; on the other hand, a venous carry over of infectious thrombi has been discussed [107], [108]. The orbital abscess, usually located intraconally in the orbit, is formed due to a diagnostic delay or an immunosuppression. A CT is usually recommended to make the diagnosis. The predictive rate for the clinical diagnosis of an orbital abscess based on the examiner is 82%; the predictive rate based on computed tomography is 91%. An MRI can be performed in cases of diagnostic uncertainty or suspected intracranial complication [109]. The therapy of a subperiosteal abscess, diagnosed in a CT, requires mandatorily an intravenous antibiotic. If the symptoms do not improve within the first 24–48 hours then a surgical drainage of the abscess is obligatory. The surgical drainage of a subperiosteal abscess is done by endoscopically opening the ethmoidal cells. In extreme cases one can also use a transfacial approach to the lateral medial orbit [110], [111]. It has been shown, based on the evidence, that a conservative therapy regimen is beneficial in young children. A prerequisite for the conservative therapy is as follows [109], [112]:

- Improvement in symptoms within 24–48 hours
- No loss in vision
- Medially located subperiosteal abscess (volume less than 0.5–1 ml)
- No systemic signs of the disease
- Age of patient younger than 2–4 years

6.1.2.2 Endocranial complications of the acute rhinosinusitis

Intracranial complication of a rhinosinusitis include the epidural, subdural and brain abscess, meningitis, cerebritis, cavernous sinus and superior sagittal sinus thrombosis. The symptoms of intracranial complications are often non-specific, such as fever, headaches, lethargy, and difficulty in concentrating. On the other hand, focal neural dysfunction of the oculomotor, trigeminal and facial nerve as well as signs of an increased intracranial pressure have priority. Endocranial complications arise from a complicated rhinosinusitis in the frontal, ethmoidal, and sphenoid sinuses. The diagnostics are usually supplemented with a CT. The CT provides more information about the defects in the osseous structures. Magnetic resonance imaging is often used to rule out a cavernous sinus thrombosis, since an MRI is more sensitive in this area. Information on the mortality of endocranial complications in the pediatric population is rare. In a study from Broberger the mortality was cited as 10–20% [112].

6.1.2.3 Complications in osseous structures of the facial skeleton

Infections in nasal sinus surgery can progress to the osseous structures of the facial skeleton. If for example an osteomyelitis is present, an extension of the infection can cause an intracranial complication. The most common osseous complications are the osteomyelitis of the maxillary and frontal sinuses, especially in childhood. Gallagher examined 125 patients with complicated ARS and found in 9% of cases an osteomyelitis [113].

6.2 Chronic rhinosinusitis (CRS)

The chronic rhinosinusitis (CRS) is a complex illness in childhood. It is often made with uncertainty, due to the overlapping of symptoms with other inflammatory diseases of the upper airways. A chronic rhinosinusitis is defined as the *inflammatory change in the nasal mucosa and nasal sinus mucosa, in which the corresponding symptoms persist for over 12 weeks*. The most common symptoms, according to the children or parents in the history taking, are the *chronic cold, rhinorrhea, nasal obstruction, and postnasal drip* [114]. In the differential diagnosis, one must consider a chronic rhinosinusitis, infection of the airways due to hyperplasia of the adenoids, adenoiditis, or even a flare-up of allergic rhinitis. The overlapping of symptoms of different diseases of the upper airways complicates diagnostic evaluation.

In comparison to adults, there is currently no reliable epidemiological prevalence data on children with chronic rhinosinusitis. According to a present study, the prevalence of chronic rhinosinusitis in adults based on self-diagnosis was around 7.5%. In 19 European centers the average prevalence was determined to be 11% [115]. Studies in the pediatric population, which examined the incidence depending on the pathological findings in computed tomography images, found in a study population of children without clinical symptoms of rhinosinusitis pathological mucosal changes in 18–45% of cases [68], [116], [117]. It was determined that the Lund-McKay score was adequate in diagnosing a CRS in children. A Lund-McKay score of 2.8 was calculated for a population of children without symptoms of rhinosinusitis, while a Lund-McKay score of 5.0 was calculated for the presence of chronic rhinosinusitis in children [118], [119].

Other studies examining the prevalence in a pediatric population, although not stating any information on incidence, determined the *age dependence in occurrence of CRS* in the different nasal sinuses. A group of children (N=196) between the ages of three and fourteen were examined. In the youngest age group a maxillary sinusitis was diagnosed in 63% of cases, a sphenoid sinusitis in 29% of cases, and an ethmoid sinusitis in 58% of cases. In the age group of 13–14 year olds an incidence of 10% for the ethmoid sinusitis, 0% for the sphenoid sinus, and 65% for the maxillary sinus was determined [120]. A risk factor to fall ill to chronic rhinosinusitis is age. In the group of two to six year olds the risk is 74%, and in the group

of over ten years old is 38% [121]. Another studies has also shown that the prevalence with increasing age (after 6–8 years) decreases [122].

Children with chronic rhinosinusitis suffer a restricted quality of life. Children that have comorbidities (such as asthma, attention deficit disorder with hyperactivity, rheumatoid arthritis, and epilepsy) in addition to chronic rhinosinusitis are especially limited. An improvement in the quality of life could be shown after functional sinus surgery or the removal of adenoids [123], [124], [125].

6.2.1 Etiologic factors in CRS

It is still presently unclear to what extent the anatomical aberrations in the ostiomeatal complex have in the development of a chronic rhinosinusitis. Although the presence of a concha bullosa, haller cell, and agger nasi cell was often diagnosed in children with chronic rhinosinusitis, the results were not compared to that of a control group. Changes to the nasal septum seem to play a minor role [126], [127].

The *microbiological findings* usually shows gram positive bacteria: *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catharrhalis*. *Staphylococcus aureus*, β -hemolytic streptococci as well as gram negative bacteria (bacteroides and fusobacterium) are also found in chronic rhinosinusitis [128], [129]. Although biofilms have been detected in adults with chronic rhinosinusitis, studies detecting biofilms in the pediatric chronic rhinosinusitis are still being awaited.

The *pathophysiological role of the adenoids* in the formation of chronic rhinosinusitis is based on the anatomical location near the nasal cavity. The adenoids comprise a *bacterial reservoir* for the formation and sustenance of chronic rhinosinusitis in children. In an electron microscope study examining the adenoids in children with chronic rhinosinusitis, a biofilm formation could be shown in 88–99% of cases [130]. In comparison, adenoids removed from children with sleep apnea showed a biofilm formation in only 6% of cases [131]. It could also be shown that swab testing of the middle meatus and the adenoids in chronic rhinosinusitis had identical bacterial cultures. The bacterial cultures grown from the adenoids have a predictive value of 91.5% for the same culture in the middle meatus [132].

6.2.2 Factors of morbidity for chronic rhinosinusitis

The allergic rhinitis is also a factor of morbidity in the pediatric population. *Information about the association between both of these illnesses varies considerably. The association to allergy varies between 40–53%* [133], [134]. Other authors could not find a correlation between radiographic findings in CT imaging and atopic status [121], [135]. A study showed positive skin prick testing in 30% of children. The prevalence did not differ from allergies in the normal population [136] (32%).

Bronchial asthma also belongs to the illnesses that can be associated with chronic rhinosinusitis in childhood. In a study from Rachelefsky, 48 children with severe asthma and comorbid chronic rhinosinusitis were treated surgically and with asthma medication. 80% of the children could reduce their asthma medication after surgical therapy [137]. Another study could also prove the concept of local asthma control through the therapy of the Rhinosinusitis [138].

The association of gastroesophageal reflux disease (GERD) and chronic rhinosinusitis in childhood has been proven in a multitude of studies. It could be shown that 63% of children with chronic rhinosinusitis have gastroesophageal reflux (by means of 24-hour pH-metry testing) [139]. Of those children, 90% benefited from a drug therapy for gastroesophageal reflux [140]. Furthermore, it could be shown in a large case-controlled study that the diagnosis of sinusitis in children with GERD was significantly higher. 4.19% of children presented with a sinusitis in comparison to the control group (1.35%) [141].

6.2.3 Forms of chronic rhinosinusitis in childhood

In the last decade, phenotyping of CRS became more common in adults. Inflammation in sinuses can be divided in CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). Diffuse bilateral nasal polyps are dominated by eosinophilic inflammation type, whereas CRSsNP mostly is dominated by neutrophilic type of inflammation [142]. Etiology of CRS is still a matter of debate, but colonization of *S. aureus* in CRSwNP is linked to asthma [143], [144]. The allergic fungal sinusitis (AFRS) in contrast is associated with fungal disease. Formation of nasal polyps in cystic fibrosis is mostly generated by bacterial infection [145].

Knowledge on AFRS in child is rare and refers to knowledge on AFRS in adults. Fungal sinusitis is substantially graded in acute invasive, chronic indolent invasive forms as in fungus ball and allergic fungal sinusitis. AFRS displays one subtype of eosinophilic CRSwNP described by Bent et al. [146] and is diagnosed by means of:

- Type IgE-mediated sensitivity (history, skin tests, specific IgE in vitro)
- Nasal polyposis
- Eosinophilic mucin (Charcot-Leyden Crystals)
- Chronic changes on CT scan (ostitis; osseous erosion)
- Fungal hyphae in the tissue with signs of invasive disease

The diagnosis of AFRS refers in childhood to adolescents and young adults: the mean age at time of diagnosis is 21.9 years. The incidence of AFRS varies due to climatic factors [147], [148]. Marple reported that children described a protracted nasal obstruction with dark coloured secretion from the nose at the first stage of disease [149], [150], [151]. Characteristic findings in CT-scan are important for further therapy. 56% of the patients had an otitis with osseous expansion and erosion of the sinuses. 70% of

children with AFRS have unilateral findings whereas in adults unilateral AFRS was found in 37% of the cases [147], [148]. A recent study reported that children with CRSwNP or AFRS are vitamin D3 deficient, which may be linked to increased dendritic cell infiltrate in tissue. Vitamin D3 is a steroid hormone that orchestrates dendritic cells in a manner similar to corticosteroids [152], [153]. In contrast to these findings the number of eosinophils and lymphocytes are reduced in CRSsNP [154].

6.2.4 Diagnosis of chronic rhinosinusitis

In the anterior rhinoscopy one should assess the middle meatus, the inferior nasal concha, the mucus secretion, and the form of the mucosa. The anterior as well as posterior rhinoscopy can be a challenge for the examiner in children. An indirect sign for posterior nasal secretion is purulent mucus discharge and cobblestone alteration on the posterior wall of the pharynx. If the children are non-compliant, the examiner is forced to rely on other findings. A skin prick test is often useful to rule out an allergic rhinitis. Recurrent infection, such as pneumonia and otitis media, can be an indication of chronic sinusitis. *The usefulness of performing a swab test to determine the bacterial spectrum is generally questionable.* Swab tests have a sensitivity of 75%, a specificity of 88.9%, a predictive value of 96%, and a negative predictive value of 85% [155], [156]. In comparison to that of adults, these results are much worse than the results of suction preparations, which show an extremely higher correlation [155].

The computed tomography is currently the imaging of choice in the diagnosis of chronic rhinosinusitis. In a prospective study with children with symptoms of chronic rhinosinusitis, it could be shown that projection radiography in 75% of cases does not correlate with the CT findings. In patients with normal findings in conventional X-ray imaging of the nasal sinuses, 45% had a pathological finding in at least one nasal sinus in the computed tomography. Inversely, 35% of patients had a pathological finding in the projection radiography with a normal finding in the CT. In this respect, CT imaging is a more sensitive method than the conventional X-ray imaging of the nasal sinuses [157], [158]. In a further study, it could be shown that the assessment of the Lund-McKay score can differentiate between diseased and non-diseased children. A Lund-McKay score of over five has a sensitivity of 86% and a specificity of 85% in determining the proper diagnosis. A Lund-McKay score of less than two has a negative predictive value for the presence of chronic rhinosinusitis [119]. *The indication for CT-imaging of the nasal sinuses is reserved for cases of chronic rhinosinusitis that have not been successfully treated with medication.* Special cases of chronic sinusitis, such as the allergic fungal sinusitis and the cystic fibrosis, are shown well in CT imaging. Magnetic resonance imaging is reserved for children with complications in the orbital area, neighboring skull base, and meninges.

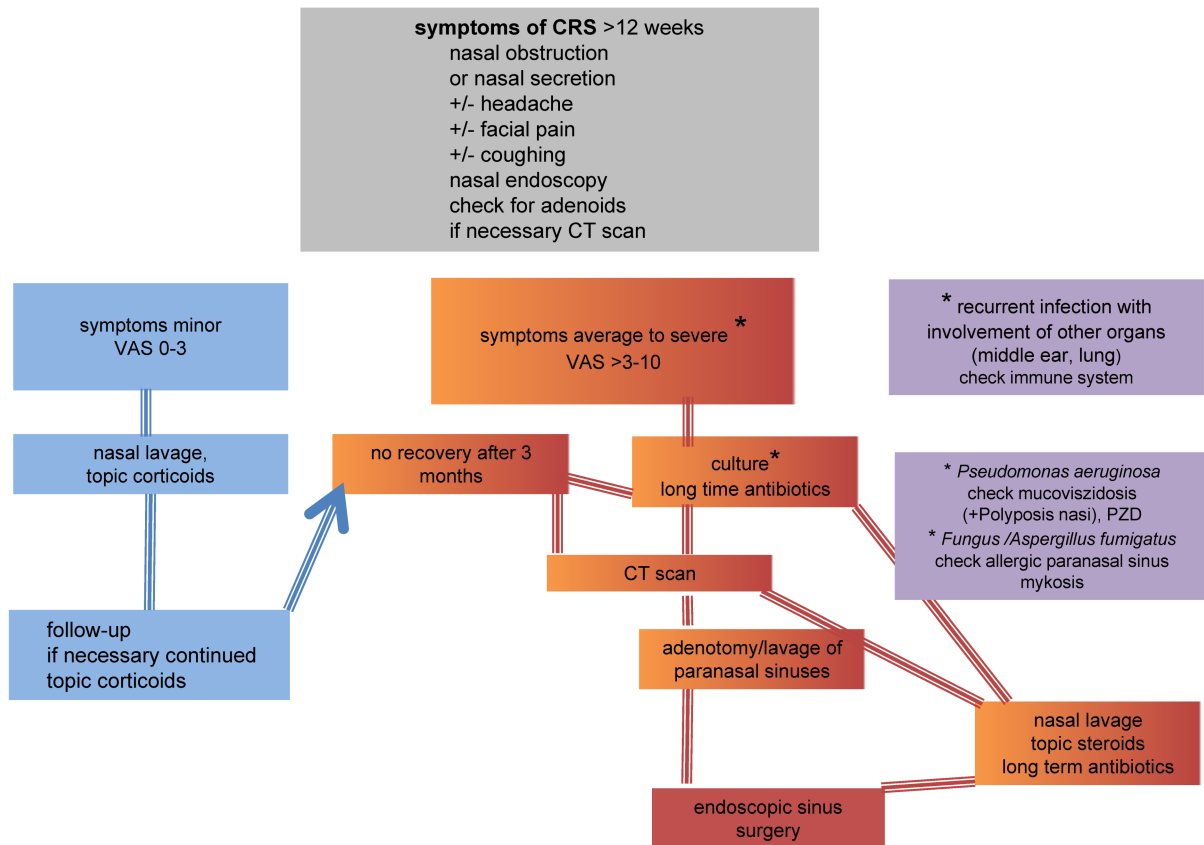


Figure 4: Management of chronic rhinosinusitis in childhood modified according to EPOS

6.2.5 Management of chronic rhinosinusitis

A staged therapeutic concept is followed in CRS based on conservative and surgical methods (Figure 4). Both therapeutic methods have not been well examined in comparison to adults. The medical therapy includes antibiotics, use of glucocorticoids (topical and systemic), as well as the use of nasal irrigation.

6.2.5.1 Antibiotic therapy

There is a total of four studies in the literature examining the effects of antibiotic therapy on CRS in children. Otten's studies from 1994 and 1988 showed no difference in the rate of healing in the therapy of a pediatric subpopulation with cefaclor versus placebo, and amoxicillin versus placebo. However, it must be noted that the description of the patient collective does not correspond to the present standard. The importance is thus greatly reduced [159], [160]. The literature also offers no evidence on the administration of short-term antibiotics in chronic rhinosinusitis in children. On the contrary, it is assumed that the use of a short-term antibiotic actually impairs the resistance. *The tendency is usually a long-term antibiotic as is usually the case in adults suffering from chronic Rhinosinusitis* [68].

Another therapy approach is the intravenous antibiotic therapy as an alternative to endoscopic nasal sinus surgery. In a retrospective analysis of 70 children between the ages of 10 months and 15 years the symptoms

completely subsided after the irrigation of the maxillary sinus and selective adenoidectomy [161]. A similar study retrospectively examined the effects of a four week intravenous antibiotic therapy after swab testing on 22 children (between the ages of 1.2–4.5) with chronic rhinosinusitis [162]. The symptoms also completely subsided in over 90% of cases. Therapy success was reportedly maintained for over 12 months. Unfortunately, both studies did not have a placebo controlled group so that *the intravenous antibiotic therapy can not be recommended. There is, up to date, no randomized control study examining the effects of intranasal glucocorticoids in children with chronic rhinosinusitis.* Nevertheless, *the topical glucocorticoid is the primary medication of choice in the therapy of pediatric CRS.* The use is based on the well examined efficacy of intranasal glucocorticoids in the therapy of adult CRS (level 1B), and the examined effectiveness and safety of intranasal glucocorticoids in the therapy of allergic rhinitis [163], [164], [165]. *The effect of a systemic steroids with methylprednisolone was examined in children eight years of age. Children received 30 days of amoxicillin/clavulanic-acid and a tapered cortisone therapy. Based on the CT Lund-McKay score, an improvement was seen in the local finding as well as the symptom score. The results of this study with systemic steroids were considerably better than the long-term results after intravenous antibiotics* [166].

6.2.5.2 Additional forms of therapy

Nasal irrigation and decongestant nasal drops are employed in all patients with chronic rhinosinusitis in order to reduce the episodes of disease. Michel showed in a randomized prospective double-blinded study that with either an isotonic salt water solution, or with decongestant nasal drops, there was an improvement in the symptom score in children 2–6 years of age [167]. Wei examined in a further study the effects of treating pediatric rhinosinusitis with a salt water solution versus a salt water solution with added gentamycin locally for six weeks [168]. Both therapy groups were equipotent in the improvement in the quality of life. There exists no data on the therapy of chronic rhinosinusitis with antihistamines and leukotriene receptor antagonists. These medications are reserved for children with allergic rhinitis [68].

6.2.6 Surgical therapy of chronic rhinosinusitis

A surgical therapy for chronic CRS is necessary when a maximal drug therapy has not improved the symptoms. Interestingly, a maximal drug regimen similar to adults is not defined. Surgical therapy of chronic rhinosinusitis includes the adenoidectomy (AT) with and without irrigation of the maxillary sinus, balloon dilatation of the maxillary sinus, and the functional endoscopic sinus surgery (FESS).

6.2.6.1 Significance of adenoidectomy with and without irrigation and balloon dilatation

Based on the assumption that adenoids are a reservoir for bacteria, from which recurrent infections of the nose and nasal sinus originate, *the adenoidectomy is still defined as a cleansing procedure in rhinosinusitis. 69.3% of the children had benefit from adenoidectomy* [169]. A current meta-analysis in a pediatric subpopulation with children younger than seven years of age and concurrent bronchial asthma showed no improvement of symptoms after adenoidectomy [170], [171]. However, the additional irrigation of the nasal sinuses in this pediatric population combined with the adenoidectomy showed a success rate of 88%. There is currently no evidence for the treatment with a long-term antibiotic after adenoidectomy [172]. The significance of the balloon dilatation is presently being arguably discussed; this is due to the fact that various studies examined the combination of methods: balloon dilatation, irrigation of the nasal sinuses, and adenoidectomy. The effects of each method could not be differentiated in these studies [170], [171].

6.2.6.2 Functional endoscopic nasal sinus surgery

Nasal sinus surgery is considered nowadays as effective and safe in children. The rate of success is according to a meta-analysis 88% and has a low complication rate [173]. The functional nasal sinus surgery is effective in the alleviation of nasal obstruction due to polyps or

concha bullosa. Improvement was determined to be 91% for nasal obstruction, 90% for rhinorrhea, 97% for headaches, 89% for hyposmia, and 96% for the chronic cold [174]. The assumption that midface growth was affected due to FESS could not be proven in long-term studies. However, in two other studies a recurrence of 39% was determined in children. Strikingly, these children had a CRS with nasal polyps and allergic rhinitis [175], [176], [177]. In summary, after failure of a conservative drug therapy in children with CRSsNP, the adenoidectomy with irrigation of the maxillary sinus (perhaps also balloon dilatation) is recommended. Children should have functional nasal sinus surgery when diseased with cystic fibrosis, nasal polyps, choanal polyps, or allergic fungal sinusitis.

7 Systemic inflammatory diseases of nose and paranasal sinuses

7.1 Primary ciliary dyskinesia (PCD)

Primary ciliary dyskinesia (PCD), or immotile cilia syndrome, is a rare inherited disorder with an autosomal recessive trait. The incidence is about 1:20,000–1:60,000 individuals. PCD is associated with a defective cilia of respiratory epithelium in lung, bronchi, nasal mucosa and middle ear, which clinically is characterized by recurrent infections of upper and lower respiratory tract due to defective mucociliary clearance [178], [179]. The coexistence of PCD and situs inversus (SI) is called Kartagener's syndrome (KS) and occurs in 40–50% of PCD patients.

Clinical severity of symptoms vary and it might account for up to 13% of all patients with bronchiectasis. The mean age at diagnosis of PCD, in a paediatric case series was 4.4 years (6 years for those without situs inversus) [180]. The assumption that KS clinically displays CRS with nasal polyps with duration of disease has not been confirmed in a longterm study with 30 children [181]. Organspecific manifestation of disease symptoms in ENT concerns 60% of paranasal sinuses and 78% of the middle ear [179], [182].

Etiology of PCD is clarified by heterogenous group of autosomal inherited disorders. Defective expression of several proteins in ciliary ultrastructure accounts for PCD. Some ultrastructural defects are located dynein arms of cilia and are result of gene mutation of coding for proteins [183] (Table 2).

Specific diagnostic work up for PCD is recommended for children with situs inversus, chronic cough, bronchiectasis and cerebral ventriculomegaly [179]. Diagnostic set up comprises several features such as examination of ciliary beat pattern and frequency analysis through high-resolution digital high-speed video (DHSV), immunofluorescence microscopy, electron microscopy and genetic analysis (Figure 5).

Treatment of PCD involves antibiotic therapy of upper and lower airway infections for more than 3 months of

Table 2: Modified list of most frequent gene defects in PCD according to Barbato et al. [179].

ODA = outer dynein arm, IDA = inner dynein arm, KS = Kartagener's Syndrome

Gene	Defective ultrastructure	Phenotype of disease
DNAH5	ODA	PCD+KS
DNAI1	ODA	PCD+KS
DNAH11	normal	PCD+KS
TXNDC3	ODA	PCD+KS
DNAI2	ODA	KS
KTU	ODA+IDA	PCD+KS
RPGR	variable	PCD +retinitis pigmentosa
OFD1	Not known	PCD+ mental retardation

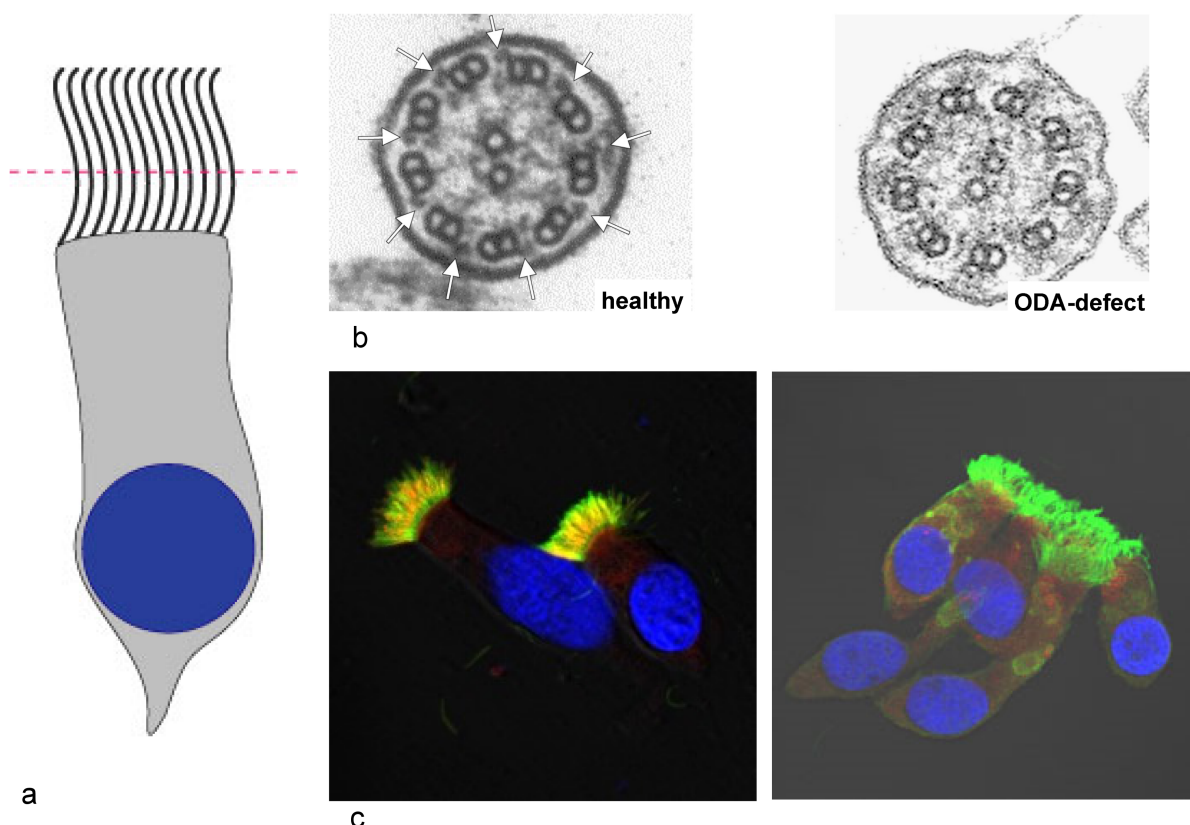


Figure 5: a) Schematic structure of cilia in respiratory epithelium. b) Electron microscopy of a cilium (healthy and with ODA-defect). c) Immunofluorescence analysis (healthy and with ODA-defect).

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duration. The most common bacteria responsible for recurrent infections are *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Intravenous antibiotic therapy is recommended, whenever symptoms are not reduced by oral therapy [184]. There is no evidence for mucolytic therapy in PCD. Interestingly, middle ear effusions are not any more commonly treated by ventilations tubes because of prolonged follow up with otorrhoe according to guidelines [179], [185]. FESS is recommended at stage of complications or worsening of symptoms [186].

7.2 Mucoviscidosis (cystic fibrosis)

The mucoviscidosis is an autosomal recessive gene defect with a mutation of the transmembrane conductance regulator gene (CTFR) in epithelial cells, which regulate the chloride ion transport in exocrine glands. Clinical symptoms are associated with changes in the composition of secretions in the exocrine glands. As a consequence, an obstruction of the excretory duct with cystic-fibrotic transformation of the involved organs is seen. Mucoviscidosis is after hemochromatosis the most common congenital metabolic disorder in caucasians with an incidence of 1 to 2,000 newborns. Every year in Germany approximately 300 children are born with mucoviscidosis. The thick mucus in combination with a blockage of secre-

tion transport due to dysfunctional cilia leads to recurrent sinusitis that is symptomatic in approximately 20% of cases. *Bilateral nasal polyps are most common in child with cystic fibrosis*. Results in a retrospective study from 1991 showed that 80% of children with cystic fibrosis had sinunasal polyps at the time of the operation. In comparison, only 16% of the children had nasal polyps diagnosed in the group with chronic rhinosinusitis without evidence of cystic fibrosis. A heterozygous mutation in the CTFR gene is with a mild form of cystic fibrosis associated, and can have a clinically normal sweat test. The rhinosinusitis in cystic fibrosis is clinically colonized by different bacterial subpopulations. In the cystic fibrosis group, 81% of the children showed *Pseudomonas aeruginosa* on the intraoperatively taken cultures [187]. In the course of an early colonization in the nasal sinuses with *Pseudomonas aeruginosa*, the bacteria acquires a phenotype that allows the survival in the lower airway tract [188], [189].

The surgical therapy also plays an important role in addition to the conservative therapy with irrigation, mucolytics and topical corticoids.

In general, the results do not differ in the functional nasal surgery in children with cystic fibrosis in comparison to adults. Patients with cystic fibrosis tend to have pronounced nasal sinus findings in CT imaging, as well as heightened preoperative and postoperative endoscopy scores in comparison to non-cystic-fibrosis patients [187]. The postoperative results document the efficacy, safety, and subjective tolerance of the surgical procedure. Another marker that was evaluated in a further study was the health status, determined based on various in-patient stays. It was shown that there was no significant difference in hospital visits; an improvement in the quality of life was figured out. Associated with the improvement in quality of life was the reduction of nasal obstruction, nasal secretion, and postnasal drip, as well as a high satisfaction in functional nasal sinus surgery [190]. Interestingly, nasal sinus surgery in combination with antimicrobial irrigation was classified as significantly better than nasal sinus surgery without irrigation in an adult population [191]. This was determined based on a postoperative observational period taking into account the timing of a second and third operation. It can be said in summary though, that randomized controlled studies are still lacking in this area of nasal sinus surgery [67].

8 Distinctiveness of the allergic rhinitis (AR) in childhood

The allergic rhinitis is an immunoglobulin (Ig)-E mediated disease of the nasal mucosa. In the present classification it is divided into an intermittent and persistent symptom form. The prevalence of allergic rhinitis has constantly risen in the last 10 years; *about 40% of children* and 10–30% of adults suffer nowadays from allergic rhinitis. In 15 years the prevalence is expected to reach 50% in Europe [192], [193], [194], [195], [196], [197], [198].

The AR is symptomatic starting at the age of four to five [199]. The prevalence at this age is around 5–9.6% and rises further in adolescence. The prevalence at the age of six to seven is noted at 7.2–8.5%. In a current study (“German Health Interview and Examination Survey for Children and Adolescents”, KIGGS) the prevalence of allergic rhinitis was 17% in the group of 13–14-year-olds [198], [200].

Comorbidities in adult age are well noted; common comorbidities in childhood include bronchial asthma, bronchial hyperreactivity, conjunctivitis, and otitis media, which can often lead to a clear limitation in the quality of life (Leynart, Weeinmaye, (prieto) Bertelson et al). It can be assumed that up to 50% of the pediatric patient population with AR also have or will develop bronchial asthma (AB) as disease continues (= change of disease level) [201], [202], [203], [204].

Pathophysiologically, it can be seen that the immune response to inhaled allergens in the pediatric population is weaker than in comparison to adults. In an advanced stage of allergic rhinitis with symptoms of long duration there is a complex immune response on the molecular level. *This offers the opportunity to treat children in an initial phase of allergic rhinitis by intervening and influencing the natural progress of the disease* [205].

The specific immune therapy is still the only causal therapy form, and offers a therapeutic approach for the possibility of a modulation of the allergic immune response – also in childhood. According to the KIGGS-Study (“German Health Interview and Examination Survey for Children and Adolescents”) 5% of children with AR and/or BA are treated with SIT (approx. 75% SCIT, 25% SLIT) [198], [200]. The allergic rhinitis is the most common diagnosis in children treated with homeopathic methods. The subcutaneous immune therapy (SCIT) in childhood is according to the current S3-guidelines indicated under the following conditions [206]:

- Proof of an IgE-mediated sensitization based on skin prick testing or in-vitro diagnostics
- A clear connection of the proven sensitization with clinical symptoms and/or corresponding provocation tests
- Availability of standardized or high quality allergen extracts
- No possibility of adequate allergen avoidance
- Proof of effectiveness of the planned SCIT for each indication

In an actualized meta-analysis reviewed the effect of SCIT in the therapy of adults and adolescents. Five studies were analyzed that included not only adults, but also young patients with seasonal AR. It could be shown that there was a significant reduction in drug consumption and symptom score within the verum group in comparison to the placebo group [207], [208]. Other randomized and placebo-controlled studies have also established the clinical efficacy of SCIT in respiratory allergies in children. However, they do not reach the evidence grade 1A. Zielen et al. showed in a recent publication (a controlled study)

that the SCIT with a house-dust-mite allergoid in asthmatic children with dust-mite allergy had a clinically relevant reduction of symptoms after two years of therapy. This was evident due to the significant improvement in asthma control and a consecutive reduction in inhaled glucocorticoids in comparison to the placebo group. There is presently no indication for the therapy of high grade asthma with SCIT [207], [208].

In addition to the SCIT, over the past decade the efficacy of the *sublingual immune therapy (SLIT)* has been examined. It could be shown in large randomized controlled studies of large pediatric collectives that the preseasonal administration of SLIT with grass pollen extract continued during the pollen season leads to a reduction of seasonal symptoms and drug usage [198], [209]. Local reactions and light systemic reactions often do occur with the SLIT therapy; however, severe anaphylactic reactions or even deaths have not been reported in SLIT performed according to guideline standards [210]. Due to this, SLIT is being nowadays increasingly propagated as an alternative to SCIT in intermittent allergic rhinoconjunctivitis. The indication criteria for SLIT do not differ from that of SCIT. However, one must bear the following in mind [206]:

- Use of SLIT in children and adolescents only with preparations of proven potency
- Age of patient should be over five for grass pollen allergies
- SLIT (as a less painful and, according to the current level of knowledge, less systemic side effect substitute) can be used as an alternative to SCIT in children, when the SCIT is not possible.

The follow-up of asthma symptoms in the SLIT in children with AR is controversially discussed in the literature. A uniform therapeutic strategy could not be determined in a meta-analysis due to heterogenic measured parameters and differences in calculated score systems in the examined studies [211]. In another study from 2009, it could be shown that the asthma symptoms with SLIT were significantly reduced, while the rescue medication in comparison to the verum group did not change [212]. Studies comparing SLIT and SCIT do not presently exist. Long term observations of SCIT have shown a duration of therapeutic effect after SCIT of 12 years; however, the results of the studies are due to lacking randomization and placebo control only of limited usage. In the PAT study, a preventive effect in the level change could be shown [213], [214], [215]. The development of sensitization to other allergens could also be shown in studies [215]. Similar results could be shown in SLIT [216], [217]. An early therapy with SIT may prevent the development of bronchial asthma and secondary sensitization to other allergens. Therefore SIT is recommended in treatment of allergic rhinitis whenever possible.

9 Primary immunodeficiency and antibody deficiency in CRS

Immunodeficiency is often considered etiologically in children with recurrent infections of the upper airways, especially when the susceptibility to infection passes a certain level. A pathological susceptibility in children can up till now not be distinguished from a physiological susceptibility to infection. In a prospective cohort study on the frequency of airway infection conducted over a period of eleven years and 5,363 person-years in Tecumseh, Michigan, USA; the physiological susceptibility to infection was dependant on age. The frequency of infection was on average 4.9 per year for the ages of 0–4, for the ages of 5–19 was 2.8 per year, for the ages 20–39 was 2.2 per year, and for over 40 years of age was 1.6 per year [218]. The frequency of infection is further dependant on factors such as social structure, size of family, or the attendance of a day care center [219]. It is not possible to set an exact cut-off for a still normal number of episodes and a pathological frequency. The following approximate values (in small children) are valid: \geq eight minor infections per year, \geq two pneumonias or severe sinusitis per year [220]. *A pathological susceptibility to infection can be a sign of primary immunodeficiency.* Primary immunodeficiencies are congenital dysfunctions of the immune system, which are according to the IUIS classification divided into 8 groups (International Union of Immunological Societies (IUIS) classification 2009). Primary immunodeficiencies belong to rare illnesses in which exact data to the prevalence, of the by now more than 170 different molecular genetic defects, is still lacking [220].

Primary immunodeficiencies are associated most often with an IgA deficiency (30%), followed by an IgG subclass deficiency (20%), and a hypogammaglobulinemia (23%). Other deficiencies are more seldom, such as the combined B and T lymphocyte deficiency disorders (11%), phagocyte deficiency (8%), and complement factor deficiency (3%) [221].

The *common variable immunodeficiency (CVID)* is the most common symptomatic immunodeficiency in humans that leads to disease. The incidence in north America and Europe is 1:25000 and 1:6600, respectively [222]. The CVID is a disease characterized with a low serum immunoglobulin concentration, defective specific antibody production, and an increased susceptibility to bacterial infection. Affected patients usually suffer from frequent respiratory airway infections accompanied with autoimmunocytopenia, lymphoproliferative syndrome, and granuloma [223].

According to Bryant et al. [224] three subgroups can be identified:

- Group A: no secretion of IgM and IgG
- Group B: secretion of only IgM
- Group C: secretion of IgM and IgG

The *selective immunoglobulin-A-deficiency (IgAD)* is characterized by low (<0.05 g/dl) or not detectable serum IgA levels in children under four years of age with normal

Table 3: Immunoglobulin therapy modification according to Hubert et al. [225]

Disease	Prevalence	Immunoglobulin status	Need for Ig substitution
Selective immunoglobulin A deficiency (IgAD)	1:800	IgA:↓ or absent, IgG and subclasses: normal, IgM: normal	no
IgG subclass deficiency	rare	IgG:↓, IgA: normal, IgM: normal	sometimes
CVID	1:66,000	IgG:↓, IgA:↓, IgM: normal or ↓	absolutely, yes
Agammaglobulinemia	very rare	IgG:↓, IgA:↓, IgM:↓	absolutely, yes

IgG levels and an intact immune response. IgG-subclass deficiencies are characterized by normal serum levels of total IgG with decreased levels of one or more IgG subclasses. *IgG subclass deficiencies* can be isolated or associated with other well-defined primary immunodeficiencies [225].

In the patient subpopulation with diagnosed CVID, the prevalence of chronic rhinosinusitis is 36–78% [222], [223]. It is reported that 41% of cases have an acute recurrent rhinosinusitis and 40% of cases a chronic rhinosinusitis [226], [227]. A laboratory parameter, indicating an immunoglobulin deficiency, represents the humoral immune response to pneumococcal vaccine. Patients with a reduced antibody titer to pneumococcal vaccine suffer in 77% of cases on a rhinosinusitis [227].

Diagnosis of primary immunodeficiency and antibody deficiency disorders is challenging and should be performed with pediatricians. Approximately 20% of the pediatric population have a IgG subclass deficiency without any clinically apparent symptoms. On the other hand, about 90% of children with IgA deficiencies are clinically symptomatic. The clinically assumed diagnosis of primary immunodeficiencies in recurrent infections should be confirmed with pathological antibody titers. A so-called diagnostic delay has been described in the literature, in which a period of 4.7–15 years can pass between the first manifestation and final diagnosis [222], [228], [229]. A radiological examination with CT can also assist in the diagnosis. Between 53% and 90% of adult and pediatric patients with an agammaglobulinemia A or with CVID have radiographic signs of chronic sinusitis in CT imaging [230]. Shapiro discovered in a prospective study that in over 50% of two to thirteen year old children had a low IgG3 level and a poor humoral immune response to the pneumococcal vaccine [231]. Another study examined the immune response of 27 children between the ages of 7 and 15 with chronic rhinosinusitis an isolated deficiency in IgA and a subclass deficiency for IgG2 and IgG3 was found [232]. Ramesh in a further study treated six patients with chronic rhinosinusitis, that had responded well to drug therapy, with intravenous immunoglobulin administration. The duration of therapy was one year. The success in therapy resulted in a decrease in drug usage and a reduction of rhinosinusitis episodes from nine to four per year; CT imaging also showed an improvement in local findings. *The authors concluded that children with chronic rhinosinusitis and an absent response to maximal*

drug therapy require investigation for a possible antibody deficiency syndrome.

Although an immunoglobulin therapy in severe forms of PID increases the total survival rate and lowers the number of life-threatening infections, it does not influence the degree of clinical CRS [223]. It was shown that in CVID patients, even after intravenous therapy, 54–63% had a chronic rhinosinusitis. Swab exams also showed a positive bacterial or viral culture in spite of intravenous administration of immunoglobulin G. The therapeutic effect of an immunoglobulin therapy in chronic rhinosinusitis has not been proven. A summary of current treatment strategies is given in Table 3. A surgical intervention in the therapy of primary immunodeficiencies has to date not been examined.

Notes

Competing interests

The authors declare that they have no competing interests.

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