

REVIEW ARTICLE

Management of chronic rhinosinusitisAlessandro Cazzavillan¹, Paolo Castelnuovo², Marco Berlucchi³, Ilaria Baiardini⁴, Andrea Franzetti⁵, Piero Nicolai⁶, Stefania Gallo² & Giovanni Passalacqua⁴

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To cite this article: Cazzavillan A, Castelnuovo P, Berlucchi M, Baiardini I, Franzetti A, Nicolai P, Gallo S, Passalacqua G. Management of chronic rhinosinusitis in children. *Pediatr Allergy Immunol* 2012; **23** (Suppl. 22): 32–44.

Keywords

chronic rhinosinusitis; children; medical treatment; surgical treatment; patient-reported outcomes.

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Accepted for publication 16 April 2012

DOI:10.1111/j.1399-3038.2012.01322.x

Abstract

Chronic rhinosinusitis (CRS) in children is difficult to treat, with resultant frequent recurrences and failures. There are controversies in the treatment, mirroring the debate over the exact etiology of this disorder. The available medical treatments are antibiotics, topical nasal corticosteroids, and nasal lavage with saline solutions; though, there is no general agreement on the efficacy of the latter. The new technique of balloon sinuplasty allows ventilation to the sinuses to be restored with minimal risk and trauma to the tissues, and initial outcome seems promising, being successful in most treated children. Concerning the surgical approach, adenoidectomy is among the most frequent surgical procedures performed on children, but its therapeutic effect is controversial, because randomized studies have failed to prove that adenoidectomy alone is sufficient in curing CRS. Instead, functional endoscopic sinus surgery is a minimally invasive technique which restores the sinus ostia patency and can re-establish ventilation and drainage through the natural pathways. It is important that the effectiveness of any treatment is also evaluated by patient-reported outcomes (PROs) that refer to all health-related reports coming from the patients, without any involvement or interpretations by physician or others. Among PROs, health-related quality of life (HRQL) is the one most widely known and used. HRQL can be measured by means of validated questionnaires, which provide scores proportional to the degree of well-being perceived by patients. Concerning diseases of the upper airway including RS, there are numerous instruments specifically designed for children and caregivers, which allow to assess the effects of treatments in a more extensive and complete manner.

Chronic rhinosinusitis (CRS) is an inflammatory process involving the mucosa of the nose and one or more sinuses. Because the mucosa of the nose and sinuses form a functional and anatomic continuum, the sinuses are always involved in nasal diseases. Of fundamental importance of the normal physiology of the paranasal sinuses are the patency of the sinus ostia, the function of the epithelial and the ciliary apparatus, and the quality and quantity of secretions (1). Any mechanical obstruction of the sinus ostia, generally consequent to an acute upper respiratory tract infection (URI) or to a persistent rhinitis or both, can modify the normal ventilation and clearance function of the paranasal sinuses, thus causing a CRS (2).

Pathophysiology and pathogenesis of CRS are still insufficiently defined and for these reasons are difficult to treat.

The diagnosis, which is largely clinical, is sometimes confused by pediatricians as allergic rhinitis or by otolaryngologist as a consequence of chronic hyperplastic adenoiditis, thus leading to inappropriate medical or surgical treatment (3). These two disorders are indeed frequently associated with CRS and cooperate in maintaining or causing partial or incomplete resolution of CRS. Symptoms, especially in children, lack specificity, but rhinorrhea, nasal congestion and obstruction, chronic cough, purulent nasal discharge, and postnasal drip are the most frequently seen. CRS is defined by a duration longer than 3 months and is one of the major causes of morbidity in the pediatric population (4). A widely accepted classification of CRS based on temporal time frames is reported by Slavin et al. (5): acute rhinosinusitis (ARS), 7 days to 4 wk; subacute rhinosinusitis (SRS), 1–3 month;

recurrent acute rhinosinusitis (RARS), more than four episodes of ARS per year; and CRS, more than 3 months.

Background for management of CRS

Histopathological investigation into sinus mucosa of young children with CRS demonstrated predominantly lymphocytic inflammation characterized by a mixed lymphocyte population, macrophages, and neutrophils, rather than eosinophilic inflammation typical of adult CRS. Differences between pediatric and adult CRS suggest differing pathogenic mechanisms or progression in the inflammatory response with protracted disease (6). Ongoing immunohistopathological studies could further define the cellular response in pediatric CRS (7). The gene expression of inflammatory mediators in the sinus mucosa of children with CRS was significantly upregulated or downregulated by at least 50% in the CRS sinus tissues (8). Tuszynska et al. (9) in a group of patients with CRS found that in mucosal inflammation, there was an evidence of osteitis and increase in inflammatory marker genes in bone tissue.

Data concerning the distribution of bacterial species in patients with CRS are not consistent. The most commonly identified bacteria were α -hemolytic *Streptococcus* (20.8%), *Haemophilus influenzae* (19.5%), *Streptococcus pneumoniae* (14.0%), coagulase-negative *Staphylococcus* (13.0%), and *Staphylococcus aureus* (9.3%) (10). Anaerobes were recovered from 8% of all isolates, but their role in CRS is still debated and unclear (11). The variability of the results of microbiologic investigations into CRS may be due to the different techniques of collection or culture methods, previous antibiotic use, and difficulty in distinguishing bacterial flora from pathogenic agents. In patients with acute exacerbations of CRS (intermittent episodes characterized by purulent nasal discharge), the usual microorganisms associated are *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*, but the role of bacterial agents is not completely clear, because the persistence of symptoms despite appropriate antimicrobial treatment supports the hypothesis that bacterial infection is not the only cause of CRS (12). The presence of bacterial biofilms has been demonstrated in several studies on CRS, this being able to explain the negative cultures found in some cases and provide some link between bacterial infection and persistence of inflammation (13, 14). Several studies have shown a relationship between nasal symptoms and asthma, and rhinitis is identified as an important risk factor of developing asthma. In approximately 25% of patients, asthma is associated with several comorbid diseases, including CRS (15). The association between CRS and asthma is supported by strong epidemiological and pathogenic evidence. The profile of inflammatory cells and inflammatory mediators seen in both conditions bears considerable similarity, with a relevant role played by eosinophils. Severe asthma is uncommon in childhood, but there is compelling evidence showing that the most severe asthma is closely associated with upper respiratory illness, especially RS. Treatment of CRS, medical or surgical or both, benefits concomitant asthma and has been shown to reduce the severity of asthma (16). Adenoid hyper-

trophy, mouth breathing, and impaired sleep are sometimes associated with the other symptoms and observed with obstructive sleep apnea syndrome (OSAS) (17). Physical examination is of limited value in distinguishing among the various causes of rhinitis. Anterior rhinoscopy is often unreliable and non-specific. For this reason, nasal endoscopy is preferred, and more reliable, fiberoptic nasopharyngeal endoscopy can be easily performed by any pediatric ear-nose-throat (ENT) service with minimal patient discomfort and allows a good evaluation of septal, turbinate, or meatal abnormalities. These areas (middle turbinate and middle meatus) should be inspected carefully concerning the quality, quantity, and site of secretions (e.g., purulence originating from the osteomeatal complex), the presence of inflammation (mucus, edema of middle meatus or ethmoid area), and the choanae, nasopharynx, eustachian tube ostium, and soft palate (18).

An ENT consultation should be considered, and it is recommended in children with CRS or after unsuccessful therapy to perform a complete otolaryngologist evaluation associated with a nasal endoscopy (19). As far as imaging is concerned, radiologic studies are not routinely needed in the initial management of patients with suspected CRS. Abnormalities of the paranasal sinuses are found frequently on conventional radiographs or CT scans also in the absence of RS, and abnormal imaging findings may persist well after symptoms' improvement (20). Routine laboratory assessment is not useful in evaluation of children with uncomplicated CRS, and bacterial culture from nasopharyngeal swab could not reflect the organisms involved in CRS. Pediatric CRS is often refractory to standard antimicrobial therapy and difficult to treat, with resultant frequent recurrences and failures and controversy in the treatment, probably due to insufficient knowledge on the exact etiology of the disease and to antibiotic resistance frequently encountered in clinical practice. The evidence for diagnosis and treatment of pediatric CRS is limited, and generally expert local consensus was used. Current consensus on treatment for CRS includes a prolonged course of a broad-spectrum β -lactamic oral antibiotic, adenoidectomy in case of failure of medical management or persistent CRS, and, in selected cases, surgical endoscopic procedure (21). In CRS, the goal of minimally invasive endoscopic surgery techniques is to re-establish sinus drainage and ventilation. Treatment protocols, which include maxillary sinus irrigation followed by long-term intravenous antibiotics, have been recently demonstrated to be an effective alternative to endoscopic surgery in cases hard to resolve (22).

The role of adenoid treatment in rhinosinusitis and otitis media

Known also as nasopharyngeal or Luschka's tonsil, adenoids are formed of lymphoepithelial tissue located in the nasopharynx, specifically at the level of its superior and posterior wall. This lymphoid tissue is not evident at birth and reaches its largest size between the age of 2 and 5 yr, occupying most of the nasopharyngeal space in many children and thus leading to difficulties in nasal breathing. During puberty, ade-

noids undergo an involution until disappearing in adult age. This is also related to the fact that, during the first years of infancy, the increase in size of the nasopharynx is slower than that of the nasopharyngeal lymphoid tissue, resulting in a decrease in the size of this airway tract. Subsequently, the nasopharynx increases, whereas adenoids remain stable or involute. This results in later enlargement of the airway (23). Adenoids play a role in the occurrence of URIs such as otitis media (OM) and RS in pediatric age. The close anatomic relationship of adenoids with the nasopharyngeal orifice of the eustachian tubes (ET) and nasal fossae (Fig. 1) may favor infections of the middle ear, nasal cavities, and sinuses. Adenoids may cause a mechanical block of tympanic ventilation and nasal breathing or act as a reservoir for pathogenic bacteria (24, 25). If the reason for middle ear and sinonasal infections owing to mechanical obstruction caused by adenoids is intuitive (i.e., the block of ear and nasal fossae causes stasis of secretion and, consequently, infection), the role of adenoid tissue as a bacterial reservoir is unclear. In 1997, Lee and Rosenfeld (24) published a study that supported this concept. During a 4-month period, recruited 84 children with a mean age of 5.7 yr were scheduled for adenoidectomy as exclusive surgery or in combination with another surgical procedure such as tonsillectomy or tympanostomy tube insertion. The results of a questionnaire, mainly focused on sinonasal symptoms and administered to child's caregiver, were correlated with adenoid bacteriology. Adenoid specimens were used to evaluate the presence and quantity of both aerobic and anaerobic bacteria. All caregivers completed the questionnaire, and the majority reported sinonasal symptoms including nasal congestion (83%), rhinorrhea (76%), and nighttime cough (74%), whereas one or more bacterial pathogens were identified from the core samples of all adenoids. In particular, group A β -hemolytic *Streptococcus*, *S. aureus*, and *H. influenzae* were the main isolated organisms. The level of sinonasal symptoms (low, medium, or high) used to differentiate patients was significantly

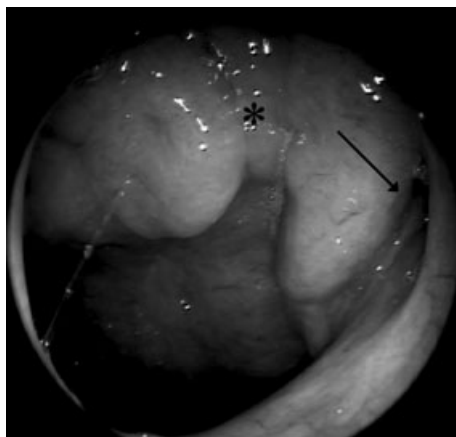


Figure 1 Endoscopic view showing the anatomic relationship of adenoids (asterisk) with the nasopharyngeal orifice of eustachian tube (arrow).

associated with quantitative bacterial results. Furthermore, the number of pathological organisms and their account reported as colony-forming units per gram of adenoid tissue showed a positive correlation with the severity of symptoms. In 2006, Zuliani et al. (26) compared the adenoid biofilms of seven children with CRS to those of nine patients affected by adenoid hypertrophy (AH). Adenoids removed from all children were examined by scanning electron microscopy. The presence of biofilms on the adenoid tissue of the RS-patients was statistically greater than in AH-children ($p < 0.001$). In 2010, Saylam et al. (27) evaluated the association between adenoid surface biofilm formation and chronic otitis media with effusion (OME) in a prospective, single-blinded study; 17 children with AH represented one group, whereas 17 patients affected by AH and chronic OME composed the other. All children underwent adenoidectomy, and the surface layer of the adenoid tissue removed was assessed for biofilm formation by scanning electron microscopy. Biofilm formation was identified in all samples. A significantly higher grade of biofilm formation was observed in the latter group with respect to the former ($p = 0.001$). There was no correlation between adenoid size and biofilm formation between groups. Recently, Nistico et al. (28) examined the differences in the adenoid biofilm in 23 children with chronic OM and 12 children affected by obstructive sleep apnea. All patients underwent adenoidectomy and adenoid specimens were analyzed by the Ibis T5000 system followed by confocal laser scanning microscopy. Among several bacteria identified in both groups, *H. influenzae* was observed in 67% of samples in the chronic otitis media group and in 10% of obstructive sleep apnea group. This difference was statistically significant ($p < 0.005$).

As suggested by the 'adenoid mediator release' theory, dysfunction of the ET can also be due to the release of chemical mediators by adenoids, which may cause inflammatory changes at the level of ET nasopharyngeal orifice and middle ear. On the basis of this hypothesis, adenoids might act as a site of allergic inflammation that influences middle ear disorders. This concept was supported by the results of a study performed by Collins et al.: By analyzing the quantity of histamine in adenoids from children with and without middle ear effusion, statistically significant higher concentrations were found in patients affected by ear disease (29). From these findings, middle ear or sinonasal cavities can benefit from the treatment of adenoids.

Adenoidectomy for otitis media

Although adenoidectomy is probably the most frequently performed surgical treatment in the pediatric population, ranging from 17/10,000 children per year in United States and Canada to 127/10,000 children per year in Belgium (30), its effectiveness in children affected by recurrent acute OM is still a matter of debate. In 1990, Paradise et al. (31) assessed the efficacy of adenoidectomy in 213 children who received tympanostomy tube placement for persistent or recurrent OM and manifested recurrent OM after tube extrusion in parallel randomized and non-randomized trials; 99 patients were allocated randomly to either an adenoidectomy group

or a control group, whereas 114 children represented the group of the separate, non-randomized but otherwise similar study, and were assigned according to the preference of caregivers. The primary outcomes were the proportion of time with OM and the number of episodes of suppurative OM. In both trials, outcomes in the adenoidectomy group were more positive than in control patients. In particular, in the randomized study, adenoidectomy subjects had significantly less time with OM than the control group and had fewer episodes than control patients. Findings in the non-randomized trial were similar to those in the randomized study: Children who underwent adenoidectomy had less time with OM and fewer episodes than the control group, but statistical significance was not achieved. These results indicated that adenoidectomy has a positive role in preventing OM.

Nine years later, Paradise et al. (32) investigated the effect of adenoidectomy and adenotonsillectomy on children affected by persistent or recurrent OM, who had not previously undergone tube placement, and compared the effectiveness of adenoid surgery alone vs. adenotonsillectomy in two parallel, randomized controlled trials; 461 children were enrolled and randomly assigned to one of two clinical studies. In the three-arm trial, 304 patients without apparent tonsillar indications for surgery were allocated to one of the following treatment groups: adenoidectomy, adenotonsillectomy, or control. In the two-arm trial, 157 children with indications for tonsillectomy were assigned to either the adenotonsillectomy or control group. The primary outcome measure was the number of episodes of acute OM during a 1-yr follow-up period. The differences in outcome between groups were small in both trials and mainly limited to the first year of follow-up. During this year, the most important difference was observed between adenotonsillectomy patients and the control group ($p < 0.001$) in the three-way trial, whereas no statistically significant differences were found when comparing the other arms in either trial. On the basis of this study, adenoid surgery cannot be considered as a first-line approach in management of recurrent acute OM.

In 2003, Mattila et al. (33) evaluated the efficacy of adenoidectomy plus tympanostomy vs. tympanostomy alone in preventing OM in children younger than 2 yr in a prospective study with both randomized and non-randomized groups; 137 subjects were included in the randomized arm and were treated with adenoidectomy and concurrent tympanostomy tube insertion (54% of the children) or with tympanostomy tube placement alone (46%), whereas 169 patients whose parents refused participation in the randomized study entered the non-randomized trial and underwent one of two aforementioned surgical procedures in relation to parent preference. The main outcome measures were the rate of acute OM episodes and their rate owing to *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* infection. The estimate of efficacy (determined as 1 minus the relative risk) in preventing OM was 0.19 and 0.25 in the randomized and non-randomized patient groups, respectively. A reduction in the rate of pneumococcal OM was observed in the randomized arm.

In 2004, Koivunen et al. (34) investigated the role of adenoidectomy vs. long-term chemoprophylaxis and placebo in

prevention of recurrent acute OM in pediatric subjects; 180 children, aged 10 months to 2 years with recurrent acute OM were enrolled in a randomized, double-blind, controlled trial, and 60 patients were allocated to each treatment group (adenoidectomy, chemoprophylaxis, or placebo). Antibiotic therapy (sulfisoxazole, 50 mg/kg daily) and placebo were given for 6 months at a similar frequency and volume. All children were followed up for 2 yr using patient diaries and clinical evaluation. The primary outcome was intervention failure observed in the first 6 months of follow-up. Intervention failure was considered if the patient suffered from two acute OM episodes for 2 months, three episodes for 6 months, or middle ear effusion for at least 2 months. Failures were observed in 25, 17, and 26 children in the adenoidectomy, antibiotic, and placebo arms, respectively, and the decrease in risk compared with the placebo group was 10% in the surgical group and 18% in the chemoprophylaxis arm. Furthermore, no significant differences among groups were identified regarding the number of episodes of acute OM, physician visits, antibiotic prescriptions, and days with signs and symptoms of airway infection. As for recurrent acute OM, the use of adenoidectomy for the treatment of OME, defined as the presence of fluid in the middle ear without sign and symptoms of acute ear infection (35, 36), has always been controversial. First published in 1994 and confirmed in 2004, the Agency for Health Care Policy and Research issued guidelines for the treatment of OME. In view of the lack of demonstrated efficacy in children younger than 4 yr of age and partial short-term positive outcomes in patients aged 3 yrs or older, adenoidectomy as a primary treatment was not recommended for uncomplicated OME unless a specific indication exists, such as nasal obstruction and chronic adenoiditis, but it was proposed instead of the insertion of a tympanostomy tube as the preferred initial surgical management (37).

Several trials have analyzed the efficacy of adenoid removal in children younger than 4 yr, older children, or both. In an old study, Maw recruited 103 patients with chronic OME aged 2–11 yr (38). All children underwent tympanostomy tube insertion associated with adenoidectomy, adenotonsillectomy, or no further surgery. More effective resolution of auricular fluid was observed in the adenoidectomy group compared to controls, but analysis based on patient age was not performed. A Canadian study examined the effect of adenoidectomy or adenotonsillectomy associated with tympanostomy tube insertion in 37,316 children, analyzing the rate of tube reinsertion. A significant reduction in tube reinsertion was observed in patients underwent adenoid surgery plus tube placement compared to those underwent tube insertion alone ($p < 0.001$), but it is worthwhile to highlight that combined surgery and tympanostomy tube insertion alone were performed in children with a median age of 4 and 2 yr, respectively (39). In 2007, Kadhim et al. (40) assessed the benefits of performing pharyngeal surgery (adenoidectomy, adenotonsillectomy, or tonsillectomy) concomitantly with tube insertion in a large cohort including 51,373 children < 10 yr of age. In this trial, the percentage of recurrent OM with effusion after surgery needing a second tube

insertion was evaluated as the primary outcome in all treatment groups. A total of 29% of patients underwent pharyngeal surgical procedures at the same time of tube insertion. The proportion of children necessitating a second tube procedure was significantly lower in both the adenoidectomy ($p < 0.001$) and adenotonsillectomy groups ($p < 0.001$) compared to children who had an ear tube procedure as their first treatment. In spite of the retrospective nature of the above-described studies, the results obtained on very large cohorts of patients suggested a positive role of adenoid surgery as primary treatment. This has been questioned by a recent study including 98 children with chronic OME that compared the efficacy of three surgical treatment combinations (myringotomy plus tympanostomy tube insertion, adenoidectomy plus myringotomy plus tympanostomy tube insertion, adenoidectomy with myringotomy) (41). Patients aged between 24 and 47 months were randomly assigned to one of the three treatment groups and were followed up for 3 yr after surgery. At each follow-up visit, signs and symptoms of acute OM, otorrhea, or OM with effusion were recorded. After surgery, middle ear effusion was observed in 18.6%, 20.6%, and 31.1% of the myringotomy plus tympanostomy tube insertion, adenoidectomy plus myringotomy plus tympanostomy tube insertion, and adenoidectomy with myringotomy groups, respectively. A larger percentage of children in the latter group required further surgery compared to the other groups. By 36 months, there were no differences in the number of further surgical procedures for ear disease needed among groups.

Adenoidectomy for RS

Chronic and recurrent pediatric RS refractory to conservative medical therapy are commonly included among the indications for adenoid removal. In 1989, Takahashi et al. (42) investigated the effect of adenoidectomy in 78 pediatric patients affected by recurrent RS: 45 children underwent adenoidectomy, and 33 were included in the control group. They were followed for 6 months by nasal endoscopy. Patients undergoing surgery showed statistically significant improvement of endoscopic nasal findings compared to control patients (56% vs. 24%, $p < 0.01$). In 1997, a retrospective study assessed the efficacy of adenoidectomy in relieving symptomatology of CRS (43). The study cohort consisted of 44 children with an age ranging from 1 to 12 yr. Signs and symptoms of RS and frequent antibiotic use were analyzed as main outcome measures. After a follow-up ranging from 5 months to 2 yr, complete clinical resolution was observed in 58% of patients, and partial improvement was reported in 21% of children.

In 1999, Ramadan evaluated the utility of adenoid surgical treatment in a prospective non-randomized trial (44); 30 children with a mean age of 6 yr were enrolled and underwent adenoid surgery for CRS. All patients were followed for 12 months after surgery, and a questionnaire was administered at least 6 months after surgery that assessed pre- and postoperative symptom status. At the 6-month follow-up visit, 47% of patients showed improvement in symptoms. In 2001, another retrospective study analyzed 70 patients with

CRS (45). All patients received parenteral antibiotics associated with concurrent adenoidectomy when medical therapy failed; 37 children with a mean age of 6 yr also underwent surgical removal of adenoids. Initial and long-term clinical response rates of the surgical group were similar to medical treatment alone. In 2004, Ungkanont and Damrongsak examined the efficacy of adenoid surgery in a group of 37 children with recurrent RS by assessing the frequency of RS before and after surgery (46). All patients underwent adenoidectomy either alone or combined with other surgical procedures (i.e., tonsillectomy and bilateral myringotomy and tube insertion) in relation to the presence of other disorders. Significant reduction in episodes per year of RS ($p < 0.001$) was observed after surgery. Ramadan investigated the role of adenoidectomy in a prospective, non-randomized study on 64 children (47). Assessment of patients was performed by a questionnaire that included major symptoms such as nasal obstruction, rhinorrhea, cough, facial pain, and headache. This evaluation was performed before the surgical procedure and at 6-month intervals after surgery. At the end of follow-up (12 months), clinical improvement was observed in 51.6% of children. Moreover, some patient-predictive factors for outcome of treatment were identified. These included the presence or absence of asthma (37% vs. 65%), the exposure or not to smoke (46% vs. 52%), and the presence or absence of allergy (54% vs. 49%). After 3 yr, Ramadan and Tiu performed a retrospective chart review of prospectively collected data on 121 children undergoing adenoidectomy for CRS (48). All patients were followed on a monthly basis for the first 3 months and then at 3-month intervals. Successful outcomes were observed in 49.6% of cases. Another interesting point, presented for the first time in this study, was the statistical analysis of failures after surgery. This subgroup included 55 patients with the age between 3 and 13 yr; 58% of children had asthma and 55% had allergy. The presence of asthma and age < 7 yr were statistically significant predictors of earlier failure. In conclusion, when choosing the management strategy, adenoidectomy with/without tonsillectomy cannot be considered as first-line intervention in children with recurrent OM not previously undergoing surgical treatment. Adenoid surgery is effective in preventing recurrent OM in children who had previously received tympanostomy tube insertion. In children younger than 2 yr, concomitant or non-concomitant adenoidectomy with insertion of tympanostomy tubes does not offer any advantage compared to simple placement of a tympanostomy tube. Adenoidectomy associated with tube insertion has significant benefits for the resolution of OME in children older than 4 yr, whereas it cannot be recommended as initial therapy in patients younger than 2 yr. In pediatric patients with refractory chronic or recurrent RS, adenoid removal can be considered a valid surgical treatment. Further trials are warranted to evaluate the benefits of intranasal steroid therapy in prevention and resolution of both OME and RS.

Topical nasal steroids and adenoids

In the latest decades, several studies have evaluated the efficacy of intranasal steroids such as beclomethasone,

flunisolide, fluticasone propionate, and mometasone furoate in children affected by AH (49–54). In these trials, chronic obstructive nasal symptoms and adenoid size were assessed before and after steroid nasal treatment. Overall, an improvement in clinical symptoms and a decrease in adenoid size were observed. However, only one trial has assessed the effects of an intranasal steroid (mometasone furoate) in children with OME in a prospective, controlled, and randomized study (54); 34 and 29 children were included in the treatment group and control groups, respectively. Patients in treatment group received intranasal mometasone furoate 100 mcg/day for 6 wk, whereas control children were followed up with no treatment. All patients were evaluated 6 wk after management. The ears were examined by otoscopy associated with tympanometry and audiometry. Unfortunately, data on the results of these examinations in the two groups were not reported. At the end of treatment, the rate of the resolution of OME in the steroid group was significantly higher in treated than in control patients (42.2% vs. 14.5%, $p < 0.001$).

Management of CRS

Pediatric CRS is difficult to treat, with resultant frequent recurrences and failures. There are controversies in the treatment, mirroring the debate over the exact etiology of this disorder (55). When the cause are bacteria, the recommended antibiotic treatment is high-dose amoxicillin or amoxicillin/clavulanate. According to the data reported from Cincinnati Children's Hospital Medical Center, 65% of the *S. pneumoniae* isolated from outpatient children settings are resistant to penicillin. The rate of *S. pneumoniae* resistance to penicillin is increasing, and failure with amoxicillin is likely to be due to resistant *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* (56). In penicillin-allergic patients, clarithromycin or azithromycin may be used. In any case, macrolides and azalides are not to be considered as standard therapeutic agents, because of the lack of data on their efficacy, and increasingly resistant *S. pneumoniae*, or both (57).

Local symptomatic treatment with topical steroids or regular saline nasal washes with hypertonic or normal physiological solutions, which facilitates the mechanical removal of mucus and increases the ciliary beat, may also be used. Anti-histamines may have benefit in some patients, but no clinical trial has demonstrated their efficacy. The efficacy of saline nasal irrigation in treating symptoms is controversial, being available studies showing no difference between nasal saline treatment and control. A discomfort was not uncommon, and 40% of babies did not tolerate nasal saline drops (58).

Adenoidectomy and minimally invasive endoscopic sinus surgery treatments are reserved to cases that did not respond to medical treatment. The rationale for adenoidectomy is to remove a chronically infected or enlarged adenoidal tissue causing nasopharyngeal obstruction. Enlarged adenoid with nasopharyngeal obstruction results in continuous mouth breathing and sleep disturbances. However, in clinical practice, the distinction between a healthy adenoid and a chronically diseased adenoid is often made only by clinical symptoms and signs showed by the child. Actually, for most

otolaryngologists, adenoidectomy is the first surgical treatment for persistent CRS associated with enlarged adenoid causing choanal and nasopharyngeal obstruction that did not respond to medical management. Although children with CRS often undergo adenoidectomy, it is not known whether adenoidectomy would have a real effect on resolution of chronic sinonasal inflammation (59). Controversy exists on the removal of enlarged or chronically infected adenoid by adenoidectomy as an effective treatment for CRS. Randomized studies have failed to prove that adenoidectomy alone is sufficient in curing CRS (48). As the adenoid is a prominent lymphoid organ in the upper respiratory airway that readily responds to infection of the nose, it could be involved in the control of airway inflammation and local immunologic response, and not in maintaining sinonasal infections/inflammation (60). Adenoidectomy reduces caregiver-reported symptoms of CRS in a majority of pediatric patients. Given its simplicity, low risk, and apparent effectiveness, adenoidectomy is often considered the first-line surgical therapy for medically refractory, uncomplicated pediatric CRS. Children with OSAS depending on adenotonsillar hyperplasia have oral and nasopharyngeal obstruction and impaired mucous drainage. These conditions could be one of the reasons for treatment failure in some cases of CRS. Children with OSAS who undergo adenotonsillectomy show a significant improvement in respiratory distress and quality of life; CRS, however, does not resolve in all these children and may be necessary an additional antibiotic therapy (61).

Balloon sinuplasty is a new technique that was recently introduced for the treatment of CRS in children. The technique allows ventilation to the sinuses to be restored with minimal risk and trauma to the tissues. The procedure was successful in 91% cases, and no complications or side effects were noted (62). The initial experience with balloon sinuplasty in children seems to be encouraging. Because there is no bone or tissue removal, the procedure seems to be suitable for use in children. Self-assessment after endoscopic surgery showed improvement of main symptoms in 76% of children with CRS (63).

Surgical approach to CRS

In the management of CRS, the greatest challenge may be deciding what, if any, surgical approach is appropriate and when to use it (64). A thorough understanding of pathophysiology, microbiology, and principles of medical and surgical management is needed to treat pediatric sinusitis patients appropriately. Any condition that alters mucociliary clearance, decreases ventilation through a patent sinus ostium, or interferes with local or systemic defense mechanisms can lead to a cycle of sinus infection that can be very difficult to clear without concurrently addressing the associated condition.

Chronic rhinosinusitis usually begins with an inciting event or process, which leads to inflammation and obstruction of sinus ostia. This leads to stasis of secretions and impaired ventilation of the sinus. Absorption of oxygen and development of negative pressure within the sinus then ensues. This draws intranasal and nasopharyngeal contents (including bac-

teria) into the affected sinus. The presence of a viral infection also inhibits ciliary function and promotes bacterial overgrowth. However, there are many predisposing factors other than a viral upper airway infection that can lead to acute or chronic RS, including allergic rhinitis, asthma, adenoid pad, gastroesophageal reflux disease, sinus structural anomalies, and systemic disorders (cystic fibrosis, primary ciliary dyskinesia, immune deficiency) (65).

The distinction from ARS is based on duration, but CRS can also be defined in the context of recurrent ARS. This definition entails six or more episodes of ARS per year, each lasting at least 10 days, with persistent changes on CT scan at least 4 wk after medical therapy and with healthy intervals between episodes (66).

The diagnosis of CRS in the pediatric population is generally more challenging than in adults for several reasons. Children are generally less able to communicate the presence and severity of symptoms. They are also prone to frequent viral upper respiratory infections with signs and symptoms difficult to distinguish from those of CRS. Furthermore, symptoms of adenotonsillar hyperplasia may overlap with CRS symptoms.

This confers a greater weight to objective examination. Nasal endoscopy, minimally invasive and well tolerated, provides an excellent look on the nasal conditions. A CT scan should be associated in all cases of medical treatment failure, suspected orbital or intracranial complications, and with a view to any surgical procedure (67).

In CRS, it is crucial to identify and treat any underlying factors that may contribute to sinus disease. Amoxicillin/clavulanate and second-generation cephalosporins were suggested as the most appropriate antibiotic agents to address the polymicrobial and resistant nature of CRS with a recommended length of treatment of 3–6 wk (68).

The role of surgical treatment is still debated. First-line surgical management usually consists of adenoidectomy to remove the adenoid pad as a bacterial reservoir for the sinuses, with a symptomatic improvement in 70–80% of cases. Middle meatal culture or maxillary sinus aspiration with irrigation may also be performed at this time, depending on the affected sinuses and surgeon preference. The role of endoscopic sinus surgery is still evolving in the pediatric population. Functional endoscopic sinus surgery (FESS) is a minimally invasive technique which restores the sinus ostia patency. This limited approach can not only re-establish ventilation and drainage through the natural pathways but also optimize wound healing, prevent unnecessary removal of growing bone, and simplify postoperative care. The use of dedicated instruments, purposely tailored on the narrow nasal spaces of pediatric population, and the gradually increased surgical experience lead to an effective functional approach with beneficial outcome in more than 80% of cases (69). Moreover, this technique can be considered safe thanks to the lack of impact on long-term facial development (70) and a low incidence of major complications (less than 1%). As pediatric RS is more frequently located at the level of the anterior compartment (anterior ethmoid, maxillary sinus) in relation to the chronological paranasal space's development, an extensive surgery is rarely required and an anterior eth-

moidectomy and maxillary antrostomy are often sufficient to definitively treat the disease. Although there is no clear consensus on when to perform FESS for CRS, the current literature does seem to support it in the following circumstances (71): (i) when maximal medical therapy, adenoidectomy, and culture-directed systemic antibiotics have all failed with persistence of sinonasal disease, (ii) when anatomic abnormalities predispose to recurrent RS by obstructing normal sinonasal drainage pathways, with frequent infections and worsening of the quality of life, (iii) in sinonasal polyposis, to facilitate application of topical steroids or as an adjunct to desensitization in aspirin-sensitive patients, with orbital or intracranial complications of sinonasal disease, with the exception of orbital cellulitis that generally responds to medical therapy. In these cases, an MR is recommended to evaluate the extension of the process, and frequently an external approach is required, combined to the endonasal endoscopic one, to drain the abscessual collections; d) in cystic fibrosis, to improve the quality of life and facilitate application of topical antibiotics with activity against *Pseudomonas aeruginosa*.

Because blood crusting and granulation tissue may cause restenosis of the osteomeatal complex after surgery, 'second-look' nasal endoscopy has been a common procedure since the inception of pediatric FESS. The advantage of postoperative endoscopic examination under general anesthesia includes a detailed inspection of the surgical site and removal of crusting, blood clots, granulation tissue or adhesions, and removal of middle meatal splints. It is usually performed 2–4 wk after surgery to allow adequate healing of the surgical site without allowing maturation of scar tissue and subsequent synechia formation (72).

In recent years, several authors pointed out that there are no definite benefits of 'second-look' nasal endoscopy, with no difference in clinical outcome, but increased risk from the need for a second general anesthesia (73). On the basis of these preliminary remarks, it is suggested to perform 'second-look' nasal endoscopy study when diffuse sinonasal polyposis is present before operation, and recurrence is strongly suspected during wound debridement and in case of revision surgery with extensive disease.

In conclusion, pediatric CRS is a condition that is not only difficult to distinguish from similar related conditions but also challenging to manage when standard conservative treatment measures fail. The limited approach of FESS is an effective treatment modality for medically refractory RS in children with a success rate of more than 80%.

We stress anyway the concept that surgery has to be performed only in selected cases with real demand, after an accurate evaluation on the patient's condition and an appropriate radiological study. In addition, because of the increased technical difficulty, only skilled surgeons in dedicated centers should approach this kind of surgery.

Patient-reported outcomes in rhinitis and rhinosinusitis

Respiratory allergy (allergic rhinitis and asthma) and RS are the most common diseases of the respiratory tract in adults

and children. Allergic rhinitis (AR) affects an average of 10–15% of the general population (74), and the peak prevalence is in childhood and adolescence. The prevalence of respiratory allergy, especially rhinitis, is constantly increasing, as clearly demonstrated by large population-based epidemiological studies. The reason for the increasing prevalence is a matter of debate, although the ‘hygiene hypothesis’ (westernization of lifestyle, increased vaccinations, less infections) seems to explain the fact, at least in part (75). AR is characterized by four classical symptoms such as rhinorrhea, sneezing, obstruction, and itching and may be associated with conjunctivitis, especially in the case of pollen-induced allergy (76). Asthma is the disease more commonly associated with AR, so that the term of united airway disease has been introduced to define this association (77). Keeping into account the patients’ perceptions and the impact on the well-being, AR is now classified as ‘mild’ or ‘moderate-severe’ and as ‘persistent’ or ‘intermittent’ (76). AR heavily affects the quality of life (QoL) of patients and in children may lead to sleep disturbance and significant impairment of the school performance.

It has been estimated that 15% to 20% of children every year suffer from RS (78). In children, RS is often a consequence of a common cold, which is followed by superimposed bacterial infection of paranasal sinuses. RS may also evolve toward more severe forms, with purulent discharge and general decline of health status. The diagnosis is essentially based on clinical symptoms, also considering that ARS is more common under the age of 6. Predisposing factors for severe forms of RS are cystic fibrosis, mucociliary dyskinesia, or immune deficiencies. Also, AR has been suggested as a risk factor for RS, because some reports described a greater occurrence of RS in patients with respiratory allergy (79), but currently, there is no definitive proof that allergy causes RS. On the other hand, it is recommended that children with RS, especially CRS, should be evaluated also for concomitant allergic sensitizations (80, 81). Otitis media, adenoid hypertrophy, sleep disturbance, and asthma (16) are important comorbidities of both RS and rhinitis, and they may be present in various associations, so that it is often difficult to establish which of them is the ‘risk factor’ or the ‘primary disease’. Certainly, if more than one disorder is present, the well-being of the patient is proportionally worsened. In parallel to the development of the pathophysiology, microbiology, diagnostic tools, and therapeutic strategies (82), it has become progressively clear that the aforementioned diseases are not only limited to the well-known physical symptoms of the target organ, but also provoke disturbances in the general well-being of the affected subjects. This means that they can alter the self-perceived health status, pose limitations in everyday activities, and may affect the school productivity or the family relations. The expression patient-reported outcomes (PROs) refers to all health-related reports coming from the patients, without any involvement or interpretations by physician or others, such as symptoms, health-related quality of life (HRQoL), illness perception, satisfaction, and adherence to treatment (83). Among PROs, HRQoL is the most widely known and used in research and clinical trials.

Health-related quality of life and its assessment

HRQoL is ‘the functional effects of an illness and its therapy upon a patient, as perceived by the patient himself’ (83). It is easy to understand that such a definition covers a broad spectrum of subjective aspects of illness and that HRQoL is at least in part independent of specific symptoms of a disease. In fact, assessing the patient’s subjective point of view offers a more comprehensive description of the impact of the disease and its therapy on everyday life (84). This approach is particularly relevant to allergic diseases, whose treatment is primarily aimed at reaching a high level of well-being for patients by minimizing the symptoms and improving physical, psychological, and social functioning.

HRQoL is assessed by means of validated questionnaires that can be generic or specific. Generic tools can be used in all health conditions and allow the comparison of HRQoL of patients affected by different diseases or patients with healthy status, while specific questionnaires focus on the aspects of health status which are relevant to patients with a specific disease or condition.

With regard to respiratory allergies, the assessment of HRQoL has been attracting a growing interest during the last 20 yr. Many questionnaires have been developed to identify the consequences of RS and asthma from the patient’s viewpoint. This subjective dimension has been also explored in pediatric age. Although generic questionnaires have also been used for this aim (85–87), specific tools have been developed for the evaluation of HRQoL in kids, children, and adolescents suffering from respiratory allergy, and also for their caregivers (88).

Health-related quality of life in children with ear–nose–throat diseases

Allergic rhinitis (and asthma) is the most studied disease in children from the point of view of HRQoL (89). There are in fact several instruments to measure the impact of respiratory allergy in children (Tables 1 and 2). The most used of them are the Pediatric Rhinoconjunctivitis QoL questionnaire (PRQLQ) and the Pediatric Asthma QoL Questionnaire (PAQLQ). From a subjective perspective, patients with AR experience troublesome nasal symptoms (i.e., rhinorrhea, congestion, sneezing, and itching) and have frequently associated ocular symptoms (i.e., redness, itching, puffy lids, tearing), headache, fatigue, and lack of concentration. This may lead to impaired school performance and/or absenteeism (90, 91). Surprisingly, despite the high prevalence of RS, and despite its impact on the general well-being, there are few validated instruments for measuring the HRQoL in children with RS (92, 93), of which the Rhinosinusitis Disability Index, a five-item pediatric questionnaire, is the most used. As for AR, also in RS it was consistently shown that the disease remarkably affects the HRQoL of children (94, 95). Of note, the paucity of studies on HRQoL in pediatric RS is probably ascribable to the fact that in children RS is usually an acute condition, whereas HRQoL instruments perform better in chronic disorders. There is also a specific questionnaire

Table 1 The most used questionnaires for QoL assessment in children and adolescents

Instrument	Disease	Age (yr)	No of items	References
Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)	Rhino-conjunctivitis	6–12	23	(111)
Adolescent Rhinoconjunctivitis Quality of Life Questionnaire	Rhino-conjunctivitis	12–17	25	(112)
Rhinosinusitis Disability Index	Rhinosinusitis			
Quality of Life in Children with Keratoconjunctivitis (QUICK)	Kerato-conjunctivitis	5–12	16	(113)
About My Asthma (AMA)	Asthma	6–14	44	(114)
Childhood Asthma Questionnaires (CAQ)	Asthma	4–7 CAQ-A	14	(115)
		8–11 CAQ-B	23	
		12–16 CAQ-C	41	
Asthma-Related Quality of Life Scale (ARQOLS)	Asthma	6–13	35	(116)
Children's Health Survey for Asthma	Asthma	5–16	48	(117)
How Are You? (HAY)	Asthma	8–12	72	(118)
Pediatric Allergic Disease Quality of Life Questionnaire (PADQLQ)	Allergic rhino-conjunctivitis, and/or asthma, and/or skin problems.	6–16	26	(119)
Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	Asthma	7–17	23	(120)
Life Activities Questionnaire for Childhood Asthma	Asthma	4–16	71	(121)
Adolescent Asthma Quality of Life Questionnaire (AAQOL)	Asthma	12–17	32	(122)

Table 2 Examples of questionnaires for caregivers/parents

Questionnaire	Target	Number of items	References
Integrated Therapeutics Group Child Asthma Short Form	Asthma	8	(123)
Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ)	Asthma	13	(124)
Children's Health Survey for Asthma (CHSA)	Asthma	48	(117)
SN-5 survey	Sinusitis	5	(92)
PAR-ENT-QoL	ENT infections	14	(125)

assessing the pediatric QoL related to tonsils and adenoid diseases. This is called the TAHSI questionnaire (95), which is composed of six subscales related to breathing, eating, infections, behavior, cost of care, and healthcare utilization. This questionnaire has been used to assess the HRQoL in children undergoing tonsillectomy, and in one study, it was shown that surgery significantly improves HRQoL according to all subscales (96). Also for sleep obstructive disorders in children, there are specific questionnaires available (97, 98), known as Obstructive Sleep Disorders-6 (OSD6) and Obstructive Sleep Apnea-20 (OSA20). Also in this case, there are studies clearly showing an improvement in sleep-related QoL after tonsillectomy (99, 100). For otitis media, the most used questionnaires are the OM-6 (101, 102) and the otitis numerical rating scale (103).

Special issues of PROs assessment in children

The development of PROs instruments has a long history dating back to the World Health Organization's broadened

definition of health as 'a state of physical, mental, and social well-being and not merely the absence of disease' (104). Furthermore, the fundamental role of patient's perspectives is now included in the advanced evidence-based medicine systems, such as the GRADE (105), which represents the best option in defining the criteria for grading evidence and developing guidelines. For the pediatric population, the extensive use of PROs and the development in the pediatric investigation plans (PIPs) should be strongly encouraged. PIPs were introduced by the European Commission to help ensure that medicines for children are included in the mainstream drug development process in Europe, rather than as an extra optional (106). It is important to clarify some aspects about PROs assessment in a pediatric population. In fact, some characteristics of children may make the questionnaires difficult to administer, and anyway some special care may be required at every stage during the evaluation process. Although most pediatric HRQoL measures have been developed for children from 6 yr and older, also for school-age children, several issues must be taken into account: (i) the ability of the child to read and understand the questions, (ii) the relevance of the item for children (i.e., before age 10 they are able to report on concrete aspects of health, but they may have problems to reliably report their emotional and social functioning), (iii) the ability of the child to use the response options. It is recommended to employ fewer response choices for younger children, three instead of four or more, or to use a visual analog scale (107), (iv) the ability to recall information over a defined period of time. Since their long-term memory, a short recall period is recommended to elicit more accurate responses, (v) the motivation and the availability of the child to fill in a questionnaire.

Debates have arisen as to whether proxies may be used to evaluate children's HRQoL. They can be the only options

used in case of preschoolers or children with psychophysical conditions that make it impossible to fill out a questionnaire. Of note, a poor correlation in the perception of QoL between children and parents has been demonstrated (108). Therefore, it is important to remember that the impact of a chronic disease on the caregiver becomes the central issue when dealing with pediatric patients. Illness management in this case must always be shared by parents and children. For this reason, it is important to evaluate the impact of the disease on parents (109), rather than on their point of view on child's HRQoL. In conclusion, PROs begin to be considered a mandatory aspect of all clinical evaluations, and it is recommended to include them, as outcomes, also in clinical trials (110). Among PROs, HRQoL is the one most widely known and used since decades. HRQoL can be measured, at a certain extent, in an objective way by means of validated questionnaires, which provide final scores proportional to the degree of the well-being perceived by patients. Concerning ENT diseases (e.g., rhinitis, RS, otitis, adenoid hypertrophy), there are numerous instruments specifically designed for children and caregivers, and there is an abundant literature showing that each disease or comorbidity affects the HRQoL of children. In addition, by means of the specific questionnaires, the effects of treatments can be evaluated in a more extensive and complete manner. This is particularly true for respiratory allergy, for which a large number of questionnaires are available. It is also true that the evaluation of HRQoL (and PROs more in general) poses special problems and requires special attention in children. Finally, PROs cannot replace the traditional and objective outcomes, such as pulmonary function in asthma or endoscopic evaluation in RS, but should be used in association with them.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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