Braz J Otorhinolaryngol. 2015;81(1):8–18

Brazilian Journal of
OTORHINOLARYNGOLOGY
www.bjorl.org

SPECIAL ARTICLE

Rhinosinusitis: evidence and experience. A summary☆

Rinossinusites: evidências e experiências. Um resumo

Wilma T. Anselmo-Lima[a,*], Eulália Sakano[b], Edwin Tamashiro[a], André Alencar Araripe Nunes[c], Atílio Maximino Fernandes[d], Elizabeth Araújo Pereira[e], Érica Ortiz[b], Fábio de Rezende Pinna[f], Fabrizio Ricci Romano[f], Francini Grecco de Melo Padua[g], João Ferreira de Mello Junior[f], João Teles Junior[h], José Eduardo Lutaif Dolci[i], Leonardo Lopes Balsalobre Filho[g], Eduardo Macoto Kosugi[g], Marcelo Hamilton Sampaio[b], Márcio Nakanishi[j], Marco César Jorge dos Santos[k], Nilvano Alves de Andrade[l], Olavo de Godoy Mion[f], Otávio Bejzman Piltcher[e], Reginaldo Raimundo Fujita[g], Renato Roithmann[e], Richard Louis Voegels[f], Roberto Eustaquio Santos Guimarães[m], Roberto Campos Meireles[h], Rodrigo de Paula Santos[g], Victor Nakajima[n], Fabiana Cardoso Pereira Valera[a], Shirley Shizue Nagata Pignatari[g]

[a] *Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP), São Paulo, SP, Brazil*
[b] *Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil*
[c] *Universidade Federal do Ceará (UFC), Fortaleza, CE, Brazil*
[d] *Faculdade de Medicina de São José do Rio Preto (FAMERP), São José do Rio Preto, SP, Brazil*
[e] *Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil*
[f] *Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil*
[g] *Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil*
[h] *Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil*
[i] *Faculdade de Ciências Médicas, Santa Casa de São Paulo (FCMSC-SP), São Paulo, SP, Brazil*
[j] *Universidade de Brasília (UnB), Brasília, DF, Brazil*
[k] *Hospital Instituto Paranaense de Otorrinolaringologia, Curitiba, PR, Brazil*
[l] *Faculdade de Medicina, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil*
[m] *Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil*
[n] *Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), São Paulo, SP, Brazil*

Available online 24 November 2014

☆ Please cite this article as: Anselmo-Lima WT, Sakano E, Tamashiro E, Nunes AA, Fernandes AM, Pereira EA, et al. Rhinosinusitis: evidence and experience. A summary. Braz J Otorhinolaryngol. 2015;81:8–18.

* Corresponding author.
E-mail: wtalima@fmrp.usp.br (W.T. Anselmo-Lima).

http://dx.doi.org/10.1016/j.bjorl.2014.11.005

Introduction

Rhinosinusitis (RS) is an inflammatory process of the nasal mucosa, and it is classified as acute (<12 weeks) or chronic (≥12 weeks) according to the time required for the evolution of signs and symptoms, and according to the severity of the condition, as Mild, Moderate or Severe. Disease severity is classified through the Visual Analog Scale (VAS) (Fig. 1), from 0 to 10 cm. The patient is asked to quantify from 0 to 10 the degree of discomfort caused by the symptoms; zero meaning no discomfort, and 10, the greatest discomfort. Severity is then classified as follows: Mild: 0–3 cm; moderate: >3–7 cm; Severe: >7–10 cm.[1]

Although VAS has only been validated for Chronic Rhinosinusitis (CRS) in adults, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012[1] also recommends its use for Acute Rhinosinusitis (ARS). There are several specific questionnaires for rhinosinusitis; however, in practice, most have limited application, particularly in acute conditions.[2–4]

Acute rhinosinusitis

Definition

Acute rhinosinusitis (ARS) is an inflammatory process of the nasal mucosa of sudden onset, lasting up to 12 weeks. It can occur one or more times within a given period, but always with complete remission of signs and symptoms between episodes.

Classification

There are several classifications for rhinosinusitis. One of the most often used is the etiological classification, which is based primarily on symptom duration:[1]

- Viral or common cold ARS: a generally self-limited condition, in which symptom duration is less than ten days;
- Post-viral ARS: when there is worsening of symptoms five days after the onset of disease, or when symptoms persist for more than ten days;
- Acute bacterial rhinosinusitis (ABRS): small percentage of patients with post-viral ARS can develop ABRS.

The viral ARS or common cold has a symptom duration that is traditionally less than 10 days. When there is symptom worsening around the fifth day, or persistence beyond ten days (and less than 12 weeks), it could be classified as a post-viral RS. It is estimated that a small percentage of post-viral ARS develops into ABRS, around 0.5–2%.

Regardless of time of duration, the presence of at least three of the signs/symptoms below may suggest bacterial ARS:

- Nasal secretion (with unilateral predominance) and presence of pus in the nasal cavity;

Figure 1 Visual Analog Scale (VAS).

- Intense local pain (with unilateral predominance);
- Fever >38 °C;
- Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels;
- ''Double worsening'': acute relapse or deterioration after the initial period of mild symptoms.

Clinical diagnosis

Signs and symptoms

At the level of primary health care and for epidemiological purposes, ARS can be diagnosed based on symptoms alone, without detailed otorhinolaryngological examination and/or imaging studies. In these cases, the distinction between types of ARS is mainly by means of medical history and physical examination performed by medical generalists and specialists, either otorhinolaryngologists or not. It is worth mentioning that, at the time of the medical assessment, patients may fail to report ''worsening'' if not asked specifically. The history of a duration of symptoms lasting a few days followed by a relapse is frequent. It is up to the assistant physician to recognize that, and in most cases, it could represent the evolution of the same disease, from a viral ARS to a post-viral one, rather than two distinct infections. Subjective evaluation of patients with ARS and its diagnosis are based on the presence of two or more of the following cardinal symptoms:[1]

- Nasal obstruction/congestion;
- Anterior or posterior nasal discharge/rhinorrhea (most often, but not always, purulent);
- Facial pain/pressure/headache;
- Olfactory disorder.

In addition to the above symptoms, odynophagia, dysphonia, cough, ear fullness and pressure and systemic symptoms such as asthenia, malaise and fever may also occur. The few studies on the frequency of these symptoms in ARS in the community have shown great variability.[5–7] The possibility of ABRS is greater in the presence of three or more of the following signs and symptoms:[1]

- Nasal secretion/presence of pus in the nasal cavity with unilateral predominance;
- Local pain with unilateral predominance;
- Fever >38 °C;
- Symptom worsening/deterioration after the initial disease period;
- Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels.

ARS symptoms have a characteristically sudden onset, without a recent history of rhinosinusitis symptoms. In the acute exacerbation of chronic rhinosinusitis (CRS), diagnostic criteria and treatments similar to those used for ARS should be used.[1] Cough, although considered an important symptom according to most international guidelines, is not one of the cardinal symptoms in this document. In the pediatric population, however, cough is identified as one of the four cardinal symptoms, rather than olfactory disorders.[1,8]

Nasal obstruction is one of the important symptoms of ARS and should be evaluated together with other patient complaints. Although methods of objective evaluation of nasal obstruction such as rhinomanometry, nasal peak inspiratory flow and acoustic rhinometry are rarely applied in daily practice in patients with ARS, studies have shown good correlation between the symptoms reported by patients and objective measurements obtained by these methods.[1]

Purulent rhinorrhea is often interpreted in clinical practice as an indicator of bacterial infection requiring the use of antibiotics.[9,10] However, the evidence for this association is limited. Despite being a symptom that seems to increase the chances of positive bacterial culture, purulent rhinorrhea alone does not characterize ABRS.[11] Purulent rhinorrhea with unilateral predominance and the presence of pus in the nasal cavity have a positive predictive value of only 50% and 17%, respectively, for positive bacterial culture obtained by maxillary sinus aspirate.[12] Therefore, the presence of purulent rhinorrhea does not necessarily indicate the existence of bacterial infection and should not be considered as an isolated criterion for antibiotic prescription.[11–13]

Reduction in the sense of smell is one of the most difficult symptoms to quantify in clinical practice and is usually evaluated only subjectively. Hyposmia and anosmia are complaints commonly associated with ARS, which can be assessed by validated objective tests and with subjective scales that exhibit good correlation.[14,15] It is important that these olfactory function tests go through the process of translation, cultural and socioeconomic adaptation to be used in different populations.[16]

Facial pain and pressure commonly occur in ARS. When unilateral, facial or even dental pain has been considered a predictor of acute maxillary sinusitis.[5,17] The complaint of dental pain in the upper teeth on the topography of the maxillary sinus showed a statistically significant association with the presence of positive bacterial culture, with a predominance of *Streptococcus pneumoniae* and *Haemophilus influenzae*, obtained by sinus aspirate.[18] However, in another study, the positive predictive value of the unilateral face pain symptom for bacterial infection was only 41%.[17]

Several studies and guidelines have sought to define the combination of symptoms that best determine the higher probability of bacterial infection and antibiotic response.[1] In the study by Berg and Carenfelt,[7] the presence of two or more findings (purulent rhinorrhea and local pain with unilateral predominance, pus in the nasal cavity and bilateral purulent rhinorrhea) showed 95% sensitivity and 77% specificity for the diagnosis of ABRS.

Clinical examination of the patient with ARS should involve, initially, the measurement of vital signs and physical examination of the head and neck, with special attention to the presence of localized or diffuse facial edema. At the oroscopy, posterior purulent secretion in the oropharynx is an important finding.[8] Anterior rhinoscopy is a part of the physical examination that should be performed in the primary evaluation of patients with nasal symptoms, and although it offers limited information, it may disclose important aspects of the nasal mucosa and secretions.[1] Fever may be present in some patients with ARS in the first days of infection,[19] and when higher than 38 °C it is considered indicative of more severe disease and may indicate the need for more aggressive treatment, especially when associated with other severe symptoms. Fever is also significantly associated with positive bacterial culture obtained by nasal aspirate especially *S. pneumoniae* and *H. influenzae*.

Despite the limited data in the literature, in patients with ARS, the presence of edema and pain on palpation of the maxillofacial region may be indicative of more severe disease, requiring antibiotics.[9]

At the primary health care levels, nasal endoscopy is generally not routinely available and is not considered a compulsory examination for the diagnosis of ARS. When available, it allows the specialist better visualization of the nasal anatomy and topographic diagnosis, as well as an opportunity to obtain material for microbiological analysis.[1] At the assessment and clinical examination of patients, possible variations between geographical regions and different populations should be considered. Climatic, social, economic and cultural differences, as well as diverse opportunity of health care access, among other factors, may change the subjective perception of the disease, as well as potentially generate peculiar clinical features. The importance of this variability is unknown from the point of view of scientific evidence; more studies are necessary to detect them.

Treatment

There is worldwide concern with the indiscriminate use of antibiotics and with the development of bacterial resistance exists worldwide. It is estimated that approximately 50 million antibiotic prescriptions for rhinosinusitis in the USA are unnecessary, being prescribed for viral infections. When the patient follows a more selective algorithm for antibiotic treatment, the benefit is greater, and it is only necessary to treat three patients for one to reach the expected result.[20] Thus, there is a worldwide trend to treat ARS according to disease severity and duration.

Antibiotics

Meta-analyses with placebo-controlled, randomized, double-blind clinical trials show the efficacy of antibiotics in improving symptoms of patients with ABRS, especially if administered carefully. They are not indicated in cases of viral rhinosinusitis, as they do not alter the disease course,[21] and should never be prescribed as symptomatic treatment, thus avoiding indiscriminate use that may contribute to increased bacterial resistance.[22]

Clinical studies have demonstrated that approximately 65% of the patients diagnosed with ABRS have spontaneous clinical resolution,[23] and in some cases mild ABRS can resolve spontaneously within the first ten days;[21] therefore, the initial adjuvant treatment, without antibiotics, may be a viable option for mild and/or post-viral RS. The introduction of antibiotics should be considered when there is no improvement after treatment with adjuvant measures or if the symptoms are increasing in severity. Antibiotics are indicated in cases of moderate to severe ABRS, in patients with severe symptoms (fever >37.8 °C and severe facial pain) and in immunocompromised patients, regardless of the disease duration, and in cases of mild or uncomplicated ABRS

that do not improve with initial treatment with topical nasal corticosteroids.[24,25]

There are no studies to define the optimal duration of treatment with antibiotics. In general, treatment duration is 7–10 days for most antimicrobial agents and 14 days for clarithromycin. Amoxicillin is considered the first choice antibiotic in primary health care centers, due to its effectiveness and low cost. Macrolides have comparable efficacy to amoxicillin and are indicated for patients allergic to β-lactam antibiotics.[22,25,26] In cases of suspected *S. pneumoniae* resistant to penicillin, severe cases and/or cases associated with comorbidities, broad-spectrum antimicrobials are indicated.

Intranasal topical corticosteroids

Patients older than 12 years with post-viral RS, or uncomplicated ABRS patients with mild or moderate symptoms,[24] and without fever or intense facial pain,[25] benefit from topical nasal corticosteroids as monotherapy. In addition to relieving the symptoms of rhinorrhea, nasal congestion, sinus pain, and facial pain/pressure,[24] topical corticosteroids minimize the indiscriminate use of antibiotics, reducing the risk of bacterial resistance.[25]

Studies have suggested that topical nasal corticosteroids associated with appropriate antibiotic therapy result in more rapid relief of general and specific symptoms of RS, especially congestion and facial pain,[27–32] accelerating patient recovery, even when there is no significant improvement in radiographic images.[30,31,33] However, the optimal dose and time of treatment are yet to be established.[28–31] Although there are no studies that compare the effectiveness of different types of nasal corticoids in ARS, many of them, such as budesonide, mometasone furoate and fluticasone propionate have shown benefits.[33] Their use is recommended for at least 14 days for symptom improvement.

Oral corticosteroids

The use of oral corticosteroids is recommended for adult patients with ABRS who have intense facial pain, as long as they have no contraindications to their use.[34,35] Oral corticosteroids should be used for three to five days, only in the first few days of the acute event, and always associated with antibiotic therapy, shortening the duration of facial pain[34] and decreasing the consumption of conventional analgesics.[35] The evaluation after 10–14 days of treatment shows that there are no significant differences in symptom resolution or treatment failure when comparing isolated antibiotic therapy with oral corticosteroids.[35] The few studies in the literature using oral corticosteroids in the treatment of ABRS have shown favorable results with methylprednisolone and prednisone.

Nasal lavage

Despite the frequent use of isotonic or hypertonic saline solution in the nasal lavage of patients with rhinitis and RS, little is known about its real benefit in ARS.

Randomized trials[36] comparing nasal lavage with physiological saline solution and hypertonic solution showed greater patient intolerance to the hypertonic solution. A meta-analysis of placebo-controlled, randomized and double-blind trials showed limited benefit of nasal irrigation with nasal saline solution in adults, in general, not demonstrating, any difference between patients and control groups. Only one study showed a mean difference of improvement in the time of symptom resolution of 0.3 days, without statistical significance.[37]

In another meta-analysis in patients younger than 18 years with ARS, there was no clear evidence that antihistamines, decongestants and nasal lavage were effective in children with ARS.[38]

Despite little evidence of clinical benefit, the use of nasal saline lavage is generally recommended in patients with ARS. It results in improved ciliary function, reduces mucosal edema and inflammatory mediators, thus helping to clean the nasal cavity of the secretions of the infectious processes, and has no reported side effects.[39]

Chronic rhinosinusitis

Definition

CRS is an inflammatory disease of the nasal mucosa that persists for at least 12 weeks. In specific cases, an isolated sinus involvement can be observed, as occurs in odontogenic sinusitis or in fungal ball. It can be divided phenotypically into two main entities: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP). Currently, there is evidence to suggest that these two entities have distinct physiopathogenic mechanisms.

CRS is a common disease in the population and studies on its epidemiological data are important to evaluate its distribution, analyze its risk factors and promote public health policies. However, such data are scarce in the literature. Additionally, different definitions and the heterogeneity of methodologies used in the studies – and, consequently, in the results obtained – make it difficult to compare data.

Clinical diagnosis

Several clinical tests have been developed for the clinical diagnosis of CRS, but in most patients it is based only on the presence of sinonasal signs and symptoms, with a duration of greater than 12 weeks.[40–42] Sinonasal endoscopy and computed tomography (CT) are complementary examinations and help in disease classification. In both the CRSwNP and CRSsNP forms, the main symptoms are:

- **Nasal obstruction**[41,42]**:** Extremely subjective symptom. It is one of the most frequent complaints in clinical practice, affecting approximately 83.7% of the patients,[43] being even more important in patients with nasal polyposis. It is caused by the congestion of sinusoidal vessels, resulting in local edema, followed by tissue fibrosis, and it subsequently only resolves with the use of vasoconstrictors. Although it is a subjective symptom, several articles in the literature have validated nasal obstruction as an important symptom of CRS, using acoustic rhinomanometry and peak nasal inspiratory flow.[44]
- **Rhinorrhea:** It can be anterior or posterior, and can vary from hyaline to mucopurulent secretion and is present in 63.6% of the patients with CRS. It may also be associated

with cacosmia, cough and hoarseness. It is a difficult symptom to validate or quantify.[43]

- **Olfactory disorders:** Hyposmia or even anosmia is frequent, especially in CRSwNP, found in up to 46% of the patients.[42,43] It can be caused by an obstructive process (polyps), mucosal edema and/or degeneration caused by the chronic inflammatory process, with or without the presence of nasal polyps,[45] or due to local surgical procedures.[40] There are several tests with excellent levels of evidence in the literature, which show olfactory disorders in patients with CRS.[15]
- **Facial pain or pressure:** Symptom with variable prevalence (18–80%).[1] It is more often found in CRSwNP, in patients with allergic rhinitis of difficult control or during exacerbation processes.[1] Rhinogenic headache is an diagnosis of exclusion, according to the International Headache Society (IHS).[1]
- **Cough:** It is a frequent symptom in childhood, often unproductive, and may be the only manifestation present in CRS. In addition to the usual symptoms, such as phlegm, pharyngeal-laryngeal irritation, dysphonia, halitosis, ear fullness, adynamia and sleep disorders should be questioned.[40–42] During the interview, it is important, in addition to the classic symptoms already described, to include questions about systemic diseases and predisposing factors that may favor the development of CRS. Personal habits such as smoking, cocaine use, exposure to toxic inhalants, type of climate in the region where the patient resides and environmental pollution should be investigated.
- **Physical examination:** Anterior rhinoscopy (with and without vasoconstrictor): it is of limited usefulness, except in cases of polyposis, when polyps can be visualized by the simple inspection of the nasal vestibule. However, it is important to describe signs such as hypertrophic inferior and middle turbinates, septal deviations or mucosal degeneration. It is worth mentioning that there are no pathognomonic signs of CRS.[1,41]
- **Oropharyngoscopy:** The presence of retropalatal mucocatarrhal secretion explains the symptom of postnasal discharge, regardless of the color.[1,41,42]

Complementary examinations

Nasal endoscopy

Nasal endoscopy allows the systematic visualization of the nasal cavity (inferior, middle and upper turbinate), nasal septum, in addition to the nasopharynx and drainage pathways, and it can be performed with and without topical nasal decongestants. The presence of polyps, mucosal degeneration, secretion, crusts, structural alterations, scars and nasal tumors may also be observed. It can be performed at baseline or at regular intervals (e.g., 3, 6, 9, and 12 months) to aid diagnosis, to supervise disease follow-up and postoperative periods, as well as to collect material for supplementary tests.[46,47]

It is important to perform a systematic assessment of the nasal cavities, such as: examination of the nasal septum, turbinates, visualization of the middle meatus, of the sphenoethmoidal recess and of the nasopharynx. It is also necessary to verify the presence of crusts, ulcerations, septal perforation, signs of nasal bleeding as well as secretions, and to exclude the possibility of associated polyposis and expansive lesions. It is very important to perform the endoscopic assessment of patients who are undergoing or have previously had surgery. The evidence of mucosal disease six months after surgery should be considered as CRS. Another factor to be taken into account in patients with previous surgery is the recirculation of mucus by not including the natural ostium of the maxillary sinus in the antrostomy. Nasal endoscopy is an examination of the utmost importance to aid diagnosis, to supervise disease follow-up and in the postoperative period, as well as to collect material for supplementary tests.

Imaging assessment

CT is the method of choice for CRS; however, it is not the first step to attain diagnosis, except in cases of unilateral signs and symptoms and suspected complication.

Bacterioscopy/sinus secretion culture

Indicated in cases refractory to treatment, and when the material collected is not contaminated. It is performed by puncture of the maxillary sinus through the canine fossa and using an endoscope, with the collection being performed in the middle meatus.[48]

Biopsy

It is important for the study and classification of the inflammatory state of the CRS and nasal polyposis and it is indicated for the differential diagnosis of autoimmune, granulomatous diseases and to rule out neoplasms (especially in unilateral cases).

Comments

The diagnostic investigation of CRS is based on the patient's natural history, signs and symptoms, endoscopic examination and CT. The latter is considered a main factor in the analysis of disease evolution and in the decision for surgical intervention. The multiple causes of CRS can only provoke manifestations in the sinonasal region, but one should remember that the nasal cavity and paranasal sinuses may reflect the onset of systemic diseases. The identification of predisposing factors and diseases associated with RS are of the utmost importance for adequate patient management.

Clinical treatment

Treatment with systemic and topical antimicrobials

The increasing perception of CRS as a multifactorial inflammatory process has been expressed clearly in the latest consensus, i.e., it is not a persistent bacterial infection.[49] This fact has led to a mandatory theoretical reassessment of antimicrobial use for the treatment of this entity. However in practice, unfortunately, it is not surprising that, this group of drugs remains as a constant part of the drug arsenal used in the everyday life of these patients, as well as persistently identified among the different proposals for the management of this disease.[50] This is possibly due to lack of both alternatives and knowledge about the presence of bacteria in the paranasal sinuses of these patients as free form

and/or biofilm. This main theoretical basis for the choice of antibiotics also suffers from tools that allow the differentiation of the actual role of the bacteria found in the paranasal sinuses, as their identification alone does not mean the presence of an infectious or inflammatory condition in response to their presence.[51] However, the identification of bacteria such as *Staphylococcus* and *Pseudomonas* at higher percentages in patients with recurrent events (postoperative) continues to perpetuate the belief that they are part of the CRS pathogenesis. For the purpose of illustration and questioning, in spite of the statistically significant analysis, it is noteworthy that in terms of percentage, the number of positive cultures in this study was high both in the group with poor outcome and in the group with favorable outcome (87% vs. 73%), and for these specific bacteria the absolute difference was of 14% (39% vs. 25%).[52]

Recent studies have investigated bacteria as necessary and accountable elements, depending on their interaction with the host, to maintain the balance of the inflammatory response. The topical use of probiotics and bacteria in an attempt to establish flora and biofilm inductors of sinonasal homeostasis is an example.[53]

Over the past five years, there has been no new dramatic evidence for the use of antimicrobials in CRS. Nevertheless, there is a recommendation for macrolide use in the long term, for instance, in the absence of elevated serum IgE.[1,54–58] Meltzer et al.,[59] in a review article, concluded there is lack of publications capable of defining a proven effective proposal for the treatment of CRS, and emphasized that, for as long as the different presentations of the disease are not well defined, several treatments will follow with limitations in result interpretation and extrapolation. They also stressed that there are signs of increased interest in the development of research; however, the simple comparison of current records of randomized controlled trials (RCTs) versus placebo, i.e., designs that are adequate for the search of such responses at the National Institute of Health (NIH – ClinicalTrial.gov) does not allow the verification of this effort. (http://clinicaltrials.gov/ct2/results). Thus, more specific inclusion and exclusion criteria, randomization, prospective design, and study control arms are required for the study of antibiotic treatment in CRS.

Comments

This is a warning regarding the frequent use of antimicrobials and the importance of being able to differentiate them among the therapeutic options for the CRS. Moreover, there is not enough information in order for their use to be completely discarded. It is necessary to find ways to identify the exact patient who could benefit from the use of antimicrobials in cases of unequivocal clinical flare-up and better identify the involved agents through culture and sensitivity testing. The choice of extended antimicrobial use in CRSwNP cases, in which there is persistence of severe symptoms that have not improved with multiple treatments, including surgery, and even so, without serum IgE elevation, still lacks proof of benefit and its possible biological effects must be carefully considered when restricting its use. There is not enough evidence, in quantitative and qualitative terms, to recommend the use of topical antibiotics for CRS with and without nasal polyposis.

Corticosteroids in chronic rhinosinusitis

Therapy with topical and/or systemic corticosteroids (CS) is a valuable resource in the treatment of CRS. This effect has been more decisively demonstrated in patients with polyposis. Although more evidence-based proof and studies are necessary, these agents are considered an adjuvant in the fight against CRS in general, especially when used topically. Their systemic administration is suggested for CRS cases with uncontrolled symptoms, in which the aim is to decrease, even temporarily, the disease impact on the patient's life. In these situations, it is recommended to use the lowest effective dose for the shortest possible time to minimize the potentially severe side effects.

Preoperative use in patients with surgical indication

Although there are differences of opinion, patients with purulent CRSsNP can receive amoxicillin clavulanate 875 mg every 12 hours or cefuroxime 500 mg every 12 hours preoperatively for 7–10 days, and maintain the treatment postoperatively for 7–21 days. In some cases, fluoroquinolones and macrolides may be prescribed.

In patients with CRSwNP, the use of oral corticosteroids for three to five days is suggested, maintaining the treatment postoperatively, depending on the extent of disease. Example: prednisolone 0.50 mg/kg/day. Irrigation of the nasal mucosa with saline (isotonic) and hypertonic solutions, with and without preservatives, is a classic and safe measure in the treatment of CRS and very useful in mobilizing secretions and hydrating the mucosa pre- and postoperatively. There is no evidence for their action as isolated treatment.[49]

Surgical treatment: techniques

Several surgical techniques have been described for patients with CRSwNP and CRSsNP, refractory to medical treatment. It is worth mentioning that there is no gold standard technique that can be applied to all cases. Due to the lack of randomized controlled trials, several aspects of surgical management remain controversial. The most important of them is the extent of surgical dissection. As a result, current guidelines, primarily based on case-series studies and expert opinion, indicate that surgical management should be individualized. The current trend in CRS with and without nasal polyposis (NP) is surgical dissection, extending as far as the extent of the disease.[1]

The most frequent surgical approach is the endonasal access. However, some cases may require external or a combined access. Examples are lateral maxillary or frontal sinus lesions, or even in cases with a lack of reliable anatomical landmarks for an exclusively endonasal approach. Regardless of the technique and instrumentation used, there is clearly a learning curve in endoscopic sinonasal surgery. It is essential that the surgeon has deep knowledge of the surgical anatomy and undergoes previous training through specific courses to learn dissection of the nose and paranasal sinuses.

The surgical treatment of CRS has expanded greatly because of the use of nasal endoscopy. The image accuracy provided by endoscopes (Optical 0 degree wide angle), as

well as their angulations (30, 45 and 70 degrees), allow the visualization of all the details and recesses of the paranasal cavities. Moreover, the development of other specific equipment and instruments for intranasal and sinus approach (e.g., dilation balloons, neuronavigator and microdebrider) allows performing surgical procedures ranging from simple dilation of the drainage ostia to complete marsupialization of paranasal sinuses into the nasal cavity.[60–62]

Postoperative treatment – topical

Several products have become available for postoperative topical treatment. They can be used at high or low volumes with high, low or negative pressure.[63] The capacity of the drug to reach the appropriate anatomical region in the paranasal sinuses has been the subject of extensive research over the past five years. The effective topical therapy depends on several factors such as application technique, postoperative sinonasal anatomy and fluid dynamics (volume, pressure, position). These combined factors seem to have significant impact on the effectiveness of topical therapy in patients' sinonasal mucosa.[64–67]

The mechanical removal of mucus, antigen, pollutants, inflammatory products and bacteria/biofilms is the aim of topical treatment. This intervention very often depends on high-volume positive-pressure solutions to supply shearing forces that can change the surface tension between liquid and air. However, the same approach may not be appropriate for the use of pharmaceutical solutions that require properties promoting complete distribution within the paranasal sinus, long time of contact with the mucosa for local absorption and minimal wastage.[63]

It is considered very important to continue medical treatment postoperatively in almost all forms of CRS. Currently, it is recommended to use nasal saline wash and topical nasal corticosteroids after sinonasal endoscopic surgery for CRS.[63,68] The drug use directly at the disease site has the advantage of allowing high local doses and minimizing side effects.[64] The distribution of the topical solution to the non-operated sinuses seems to be limited. Thus, sinonasal endoscopic surgery is essential to allow effective topical distribution to the paranasal sinuses.[1] Postoperative distribution is superior with high-volume positive-pressure devices.[65–67] Low-volume sprays and drops have poor distribution and should be considered as treatment only for the nasal cavity, especially before sinonasal endoscopic surgery. There are limited data on the exact amount necessary to allow complete distribution. Nasal lavage with isotonic saline solution may be used in the immediate CRS postoperative period, as well as topical nasal corticosteroids, which may be started two to three weeks after surgery, or after crust disappearance. There are no relevant data in the literature to support the postoperative use of other nasal topical agents in CRS.

Postoperative treatment – systemic

Corticosteroids (CS). After the surgical treatment of CRS, systemic corticosteroids (CS) can be used in basically two ways: in short doses, of between seven and 14 days, with dose maintenance for the entire treatment, or for longer periods, using tapering doses.[69,70] The primary role of the CS in this type of disease is to reduce mucosal inflammation, thus providing better surgical outcomes. However, use of this medication is still avoided by many surgeons due to their potential side effects.

Antibiotics. The purpose of antibiotic use postoperatively is to prevent infection of the secretions retained in the paranasal sinuses immediately after surgery. If there is purulent secretion during the surgical procedure, antibiotics should be prescribed, based on the culture and sensitivity testing. Otherwise, antibiotics effective against the most common pathogens should be employed.[70]

Despite the scarcity of literature data on antibiotic effectiveness in the postoperative period of endoscopic sinonasal surgery, it is believed that they can improve symptoms and endoscopic appearance, if used for a longer period (at least 14 days), but there are no conclusive data about the duration of these benefits. In general, penicillin derivatives, particularly amoxicillin + clavulanic acid and cefuroxime axetil are the agents most often used.

Special aspects of rhinosinusitis in children

Diagnosis

The clinical diagnosis of ARS in children is not easy to attain. Many symptoms are common to other childhood diseases such as colds, flu and allergic rhinitis. Additionally, there are limitations and difficulties related to the clinical examination in the pediatric population.

Most common signs and symptoms

Studies in children with ARS show that the clinical picture often includes fever (50–60%), rhinorrhea (71–80%), cough (50–80%) and pain (29–33%),[71] plus retronasal secretion and nasal obstruction.[72] In children up to preschool age, the pain symptom has a low prevalence, being replaced by coughing. As for schoolchildren and adolescents, pain as a symptom becomes more common.

Although there are not many studies, most medical professionals and guidelines recommend that the diagnosis of bacterial ARS be clinical, based on the time of evolution (URTI symptoms for more than 10 days), the abrupt onset of high-intensity symptoms (as early as in the first 4 days), or symptom worsening after an initial period of improvement during a URTI, known as double worsening. The following may be part of the signs and symptoms: high fever, profuse nasal purulent discharge, periorbital edema and facial pain.[1,72–76]

Clinical examination

In addition to the abovementioned signs and symptoms, nasal endoscopy helps in diagnosing and differentiating between viral and bacterial disease, enhancing the visualization of nasal secretion and the nasopharynx. When positive for ABRS (purulent secretion draining from the middle meatus), the diagnosis is confirmed. However, purulent secretions are not always easy to visualize in children. Moreover, despite the high specificity, it has a low degree of

sensitivity, as a negative test does not exclude the diagnosis of ABRS.

Imaging study

There is a near consensus in all the most recent guidelines that the diagnosis of ARS should not be based on radiological studies, particularly on plain radiographs.[1,73,76]

Viral processes in children often involve the sinuses. Children exhibiting symptoms of URTI with at least six days duration of the clinical picture usually show signs of abnormality in all sinuses: maxillary and ethmoid, sphenoid and frontal, in order of frequency. The opacification is nonspecific and may occur in viral, bacterial and allergic processes, as well as in tumors, or even due to sinus nonformation in particular.

CT studies in children with a clinical picture suggestive of ARS showed that even the most important findings show significant regression of alterations after two weeks.[77] Indications for CT in acute sinus conditions should therefore be reserved for patients who do not improve and whose symptoms persist after appropriate therapy, as well as those with suspected complications.[74]

Drug treatment of ARS in children

Most are self-limited, resolving spontaneously.[1]

Antibiotic therapy

Results of meta-analysis suggest that the rate of improvement and resolution in ARS between 7 and 15 days is slightly higher when antibiotic therapy is used.[78] For this reason, it is believed that antibiotics should be reserved for more severe cases or when there are concomitant diseases present that could be exacerbated by ARS, such as asthma and chronic bronchitis.[1,73,75] However, there is no universal consensus regarding antibiotic use in ARS. In general, amoxicillin (40 mg/kg/day or 80 mg/kg/day) is still indicated as a reasonable initial treatment in most studies. Amoxicillin/clavulanate and cephalosporins are considered good options against beta lactamase producers[1] and are indicated in cases of first treatment failure.

Similar to the recommendations for acute otitis media, in ARS there is also the option of a single dose of ceftriaxone 50 mg/kg IV (intravenous) or IM (intramuscular) for children who are vomiting and thus unable to tolerate oral medication.[11–13] If there is clinical improvement in 24 h, treatment is completed with oral antibiotics.[75]

For penicillin-allergic patients, there is some controversy among the latest international guidelines. Some consider trimethoprim/sulfamethoxazole, macrolides and clindamycin good first choices[1] in these situations. Others do not recommend the use of trimethoprim/sulfamethoxazole and macrolides due to the increasing resistance of *Pneumococci* and *H. influenzae* to these drugs, and suggest a quinolone, such as levofloxacin, as an alternative, especially in older children, even in view of toxicity, high cost and emerging resistance.[79,80] There are no reviews on the optimal treatment duration. Recommendations based on clinical observations have shown varied results, from 10 to 28 days of treatment. One suggestion has been to maintain therapy for seven days after symptom resolution.[81]

Intranasal corticosteroids

Intranasal CS for three weeks associated with the antibiotic seems to have advantages when compared to treatment of ARS in children and adolescents with antibiotic alone, especially in relation to cough and nasal discharge.[28,35,38] There is also some evidence, based on a single double-blind, randomized trial, that in patients older than 12 years, a double dose of intranasal CS as a single drug may be more effective in controlling the ARS than the antibiotic therapy alone.[28]

Recurrent ARS (RARS)

Most authors agree that RARS is defined by acute episodes lasting less than 30 days, with intervals of at least 10 days with a completely asymptomatic patient. According to some authors, the patient should have at least four episodes a year to meet the criteria for recurrence.[75]

As in chronic conditions, one should seek to rule out some causes of systemic origin. The investigation should include allergic processes, by performing specific tests; immunoglobulin deficiencies, with quantitative research, particularly IgA and IgG; cystic fibrosis; gastroesophageal reflux, and ciliary diseases.[82] Pharyngeal tonsil hypertrophy, even mild, should also be considered, since it can act as a reservoir for pathogens. Anatomical factors, although usually not relevant in children, should also be ruled out (concha bullosa, septal deviation, etc.). In these cases, CT, nasal endoscopy and/or magnetic resonance imaging (MRI) may aid in the diagnosis of the obstructive process and of malformation.

The bacteriology is the same as for ARS and, therefore, the treatment of the acute phase should follow the same principles.[83] Unfortunately, it is necessary to recognize that the frequent use of antibiotics at short intervals can contribute to bacterial resistance. Prophylaxis with antimicrobials should be reserved for exceptional cases, usually those with confirmed underlying diseases, particularly immunodeficiencies.

The following overall prophylactic measures are recommended: annual vaccination for influenza and pneumococcal vaccine. In cases where allergic rhinitis or gastroesophageal reflux are associated, the frequency of acute events decreases when the associated disease is treated. Several studies have demonstrated that immunostimulatory medications such as bacterial lysates help control recurrent viral and bacterial RTIs, and may be an adjunct therapy in the control of RARS.[84]

Particularities of chronic rhinosinusitis in children

CRS in children is not as frequently studied as it is in adults and its prevalence has not yet been fully established. It is believed that several factors contribute to the disease, including inflammatory and bacteriological factors, and that the pharyngeal tonsil is an important factor in this age group. Treatment is primarily with drugs, and surgical therapy is reserved for the minority of patients.

Clinical and diagnostic picture

The clinical diagnosis of chronic rhinosinusitis in children is still considered a challenge, as it often overlaps those of other common childhood diseases, such as viral infections of the upper respiratory tract, hypertrophy, with or without infection of the pharyngeal tonsils and adenoids and allergic rhinitis. The most important signs and symptoms include nasal blockage/obstruction/congestion, rhinorrhea (anterior/posterior), ± facial pain/pressure, cough ± and/or endoscopic signs of disease. CT can show relevant changes in the paranasal sinuses.[1]

Imaging studies

Studies that have assessed the incidence of abnormalities in the paranasal sinuses on CT, obtained for clinical reasons unrelated to the CRS in children have shown a percentage of sinus radiographic abnormalities ranging from 18%[2,3] to 45%, percentages that are similar to those found in children with CRS symptoms. This demonstrates that the significance of an imaging study is relative and must always be considered together with the clinical picture.

Bacteriology

There are few studies on the bacteriology of CRS in children. Microorganisms that have already been found in aspirates or intraoperatively include: S. alpha hemolytic and *Staphylococcus aureus*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, as well as anaerobic organisms such as bacteroides and Brook I fusobacterium.[85–87]

Treatment

Drug treatment

Current studies demonstrate that the treatment of CRS in children with antibiotics for a short period of time is not justifiable.[1] On the other hand, both nasal CS and saline solution have shown benefits, and are considered first-line treatments for this disease, with or without the presence of polyps.[88,89]

Surgical treatment

The surgical approach should always be reserved for special cases, i.e., children who have not responded to appropriate medical treatment. Studies have shown significant improvement in the clinical picture and in quality of life, without negative repercussions in relation to facial osteoskeletal sequelae.[90] Unfortunately, the majority of studies supporting this recommendation do not have a prospective, randomized design. In general, the surgical approach, when indicated, may consist initially of an adenoidectomy,[90] with maxillary sinus lavage.[91] Surgery can be performed with or without balloon dilation,[92,93] followed by paranasal sinus endoscopic surgery in case of symptom recurrence.[94] In cases of children with cystic fibrosis, NP, antrochoanal polyps or allergic fungal RS, endoscopic surgery is the first option. Perhaps future studies comparing the different methods of treatment with standardized symptom questionnaire, pre- and postoperatively, can guide the best therapeutic approach in pediatric patients with CRS.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis 4and nasal polyps 2012. Rhinol Suppl. 2012;23:1–298.
2. Kosugi EM, Chen VG, Fonseca VMGD, Cursino MMP, Mendes Neto JA, Gregorio LC. Translation, cross-cultural adaptation and validation of SinoNasal Outcome Test (SNOT): 22 to Brazilian Portuguese. Br J Ophthalmol. 2011;77:663–9.
3. Hopkins C. Patient reported outcome measures in rhinology. Rhinology. 2009;47:10–7.
4. Morley AD, Sharp H. A review of sinonasal outcome scoring systems – which is best? Clin Otolaryngol. 2006;31:103–9.
5. Williams JW Jr, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis. Making the diagnosis by history and physical examination. Ann Intern Med. 1992;117:705–10.
6. Damm M, Quante G, Jungehuelsing M, Stennert E. Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. Laryngoscope. 2002;112:310–5.
7. Spector SL, Bernstein IL, Li JT, Berger WE, Kaliner MA, Schuller DE, et al. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol. 1998;102:S107–44.
8. Rosenfeld RM, Andes D, Bhattacharyya N, Cheung D, Eisenberg S, Ganiats TG, et al. Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg. 2007;137:S1–31.
9. Hansen JG. Management of acute rhinosinusitis in Danish general practice: a survey. Clin Epidemiol. 2011;3:213–6.
10. Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Allergy Asthma Clin Immunol. 2011;7:2.
11. Lacroix JS, Ricchetti A, Lew D, Delhumeau C, Morabia A, Stalder H, et al. Symptoms and clinical and radiological signs predicting the presence of pathogenic bacteria in acute rhinosinusitis. Arch Otolaryngol. 2002;122:192–6.
12. Lindbaek M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. Fam Med. 1996;28:183–8.
13. Lindbaek M, Hjortdahl. The clinical diagnosis of acute purulent sinusitis in general practice-a review. Br J Gen Pract. 2002;52:491–5.
14. Cain WS. Testing olfaction in a clinical setting. Ear Nose Throat J. 1989;68:22–8.
15. Cardesin A, Alobid I, Benitez P, Sierra E, de Haro J, Bernal-Sprekelsen M, et al. Barcelona Smell Test - 24 (BAST-24): validation and smell characteristics in the healthy Spanish population. Rhinology. 2006;44:83–9.
16. Fornazieri MA, Doty RL, Santos CA, Pinna FR, Bezerra TFP, Voegels RL. A new cultural adaptation of the University of Pennsylvania Smell Identification Test. Clinics. 2013;68:65–8.
17. Berg O, Carenfelt C. Analysis of symptoms and clinical signs in the maxillary sinus empyema. Arch Otolaryngol. 1988;105:343–9.
18. Hansen JG, Hojbjerg T, Rosborg J. Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population. APMIS. 2009;117:724–9.
19. Gwaltney JM Jr, Hendley JO, Simon G, Jordan WS Jr. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. JAMA. 1967;202:494–500.

20. Young J, De Sutter A, Merenstein D, van Essen GA, Kaiser L, Varonen H, et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. Lancet. 2008;371:908–14.
21. Merenstein D, Whittaker C, Chadwell T, Wegner B, D'Amico F. Are antibiotics beneficial for patients with sinusitis complaints? A randomized double-blind clinical trial. J Fam Pract. 2005;54:144–51.
22. Benninger MS, Sedory Holzer SE, Lau J. Diagnosis and treatment of uncomplicated acute bacterial rhinosinusitis: summary of the Agency for Health Care Policy and Research evidence-based report. Otolaryngol Head Neck Surg. 2000;122:1–7.
23. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicilin, and placebo. J Allergy Clin Immunol. 2005;116:1289–95.
24. de Ferranti SD, Ioannidis JP, Lau J, Anninger WV, Barz M. Are amoxicillin and folate inhibitors as effective as other antibiotics for acute sinusitis? A meta-analysis. BMJ. 1998;317:632–7.
25. Ip S, Fu L, Balk E, Chew P, Devine D, Lau J. Update on acute bacterial rhinosinusitis. Evid Rep Technol Assess (Summ). 2005;124:1–3.
26. Tan T, Little P, Stokes T, Guideline Development Group. Antibiotic prescribing for self limiting respiratory tract infections in primary care: summary of NICE guidance. BMJ. 2008;337: a437.
27. Small CB, Bachert C, Lund VL, Moscatello A, Nayak AS, Berger WE. Judicious antibiotic use and intranasal corticosteroids in acute rhinosinusitis. Am J Med. 2007;120:289–94.
28. Barlan IB, Erkan E, Bakir M, Berrak S, Basaran M. Intranasal budesonide spray as an adjunt to oral antibiotic therapy for acute sinusitis in children. Ann Allergy Asthma Immunol. 1997;78:598–601.
29. Yilmaz G, Varan B, Yilmaz T, Gürakan B. Intranasal budesonide spray as an adjunct to oralantibiotic therapy for acute sinusitis in children. Eur Arch Otorhinolaryngol. 2000;257: 256–9.
30. Meltzer EO, Charous L, Busse WW, Zinreich J, Lorber RR, Danzig MR. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. J Allergy Clin Immunol. 2000;106:630–7.
31. Nayak AS, Settipane GA, Pedinoff A, Charous L, Meltzer EO, Busse WW, et al. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. Ann Allergy Asthma Immunol. 2002;89:271–8.
32. Dolor RJ, Witsell DL, Hellkamp AS, Williams JW Jr, Califf RM, Simel DL, et al. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. JAMA. 2001;286:3097–105.
33. Meltzer EO, Orgel A, Backhaus JW, Busse WW, Druce HM, Metzger J, et al. Intranasal flunisolide spray as an adjunt to oral antibiotics therapy for sinusitis. J Allergy Clin Immunol. 1993;92:812–23.
34. Gehanno P, Beauvillain C, Bobin S, Chobaut JC, Desaulty A, Dubreuil C, et al. Short therapy with amoxicillin-clavulanate and corticosteroids in acute sinusitis: results of a multicentre study in adults. Scand J Infect Dis. 2000;32:679–84.
35. Klossek JM, Desmonts-Gohler C, Des-landes B, Coriat F, Bordure P, Dubreuil C, et al. Treatment of functional signs of acute maxillary rhinosinusitis in adults. Efficacy and tolerance of administration of oral prednisone for 3 days. Presse Med. 2004;33:303–9.
36. Adam P, Stiffman M, Blake RL Jr. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. Arch Fam Med. 1998;7:39–43.
37. Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. CDS Rev. 2010. CD006821.
38. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. CDS Rev. 2012;9. CD007909.
39. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. Laryngoscope. 2000;110:1189–93.
40. Fokkens W, Lund V, Mullol J, European Position Paper on Rhinosinusitis and Nasal Polyps Group. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl. 2007;20:1–136.
41. Marple BF, Stankiewicz JA, Baroody FM, Chow JM, Conley DB, Corey JP, et al. Diagnosis and management of chronic rhinosinusitis in adults. Postgrad Med. 2009;121:121–39.
42. Bhattacharyya N. Clinical and symptom criteria for the accurate diagnosis of chronic rhinosinusitis. Laryngoscope. 2006;116:1–22.
43. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe – an underestimated disease. A GA(2)LEN study. Allergy. 2011;66: 1216–23.
44. Numminen J, Ahtinen M, Huhtala H, Rautiainen M. Comparison of rhinometric measurements methods in intranasal pathology. Rhinology. 2003;41:65–8.
45. Hox V, Bobic S, Callebaux I, Jorissen M, Hellings PW. Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. Rhinology. 2010;48:426–32.
46. Hughes RG, Jones NS. The role of nasal endoscopy in outpatient management. Clin Otolaryngol Allied Sci. 1998;23:224–6.
47. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. Otolaryngol Head Neck Surg. 2010;143:147–51.
48. Araujo E, Dall C, Cantarelli V, Pereira A, Mariante AR. Microbiologia do meato médio na rinossinusite crônica. Rev Bras Otorrinolaringol. 2007;73:549–55.
49. Diretrizes Brasileiras de Rinossinusites. Rev Bras Otorrinolaringol. 2008;74:6–59.
50. Dubin MG, Liu C, Lin SY, Senior BA. American Rhinologic Society member survey on ''maximal medical therapy'' for chronic rhinosinusitis. Am J Rhinol. 2007;21:483–8.
51. Pandak N, Pajić-Penavić I, Sekelj A, Tomić-Paradžik M, Cabraja I, Miklaušić B. Bacterial colonization or infection in chronic sinusitis. Wien Klin Wochenschr. 2011;123:710–3.
52. Cleland EJ, Bassiouni A, Wormald PJ. The bacteriology of chronic rhinossinusitis and the pre-eminence of *Staphylococcus aureus* in revision patients. Int Forum Allergy Rhinol. 2013;3:642–6.
53. Cleland EJ, Drilling A, Bassiouni A, James C, Veugrede S, Wormald PJ. Probiotic manipulation of the chronic rhinossinusitis microbiome. Int Forum Allergy Rhinol. 2014;4:309–14.
54. Piromchai P, Kasemsiri P, Laohasiriwong S, Thanaviratananich S. Chronic rhinosinusitis and emerging treatment options. Int J Gen Med. 2013;6:453–64.
55. Adelson RT, Adappa ND. What is the proper role of oral antibiotics in the treatment of chronic sinusitis? Curr Opin Otolaryngol Head Neck Surg. 2013;21:61–8.
56. Soler ZM, Oyer SL, Kern RC, Senior BA, Kountakis SE, Marple BF, et al. Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations. Int Forum Allergy Rhinol. 2013;3:31–47.
57. Mandal R, Patel N, Ferguson BJ. Role of antibiotics in sinusitis. Curr Opin Infect Dis. 2012;25:183–92.
58. Piromchai P, Thanaviratananich S, Laopaiboon M. Systemic antibiotics for chronic rhinosinusitis without nasal polyps in adults. CDS Rev. 2011. CD008233.
59. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc. 2011;86:427–43.

60. Dalgorf DM, Sacks R, Wormald PJ, Naidoo Y, Panizza B, Uren B, et al. Image-guided surgery influences perioperative from ESS: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2013;149:17–29.
61. Ahmed J, Pal S, Hopkins C, Jayaraj S. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis. CDS Rev. 2011. CD008515.
62. Naidoo Y, Bassiouni A, Keen M, Wormald PJ. Long-term outcomes for the endoscopic modified Lothrop/Draf III procedure: a 10-year review. Laryngoscope. 2014;124:43–9.
63. Harvey RJ, Psaltis A, Schlosser RJ, Witterick IJ. Current concepts in topical therapy for chronic sinonasal disease. J Otolaryngol Head Neck Surg. 2010;39:217–31.
64. Moller W, Schuschnig U, Celik G, Munzings W, Bartenstein P, Haussinger P, et al. Topical Drug delivery in chronic rhinosinusitis patients before and after sinus surgery using pulsating aerosols. PLoS ONE. 2013;6:e74991.
65. Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadavers in us irrigation. Otolaryngol Head Neck Surg. 2008;139:137–42.
66. Snidvongs K, Chaowanapanja P, Aeumjaturapat S, Chusakul S, Praweswararat P. Does nasal irrigationenter paranasal sinuses in chronicrhinosinusitis? Am J Rhinol. 2008;22:483–6.
67. Grobler A, Weitzel EK, Buele A, Jardeleza C, Cheong YC, Field J, et al. Pre- and postoperative sinus penetration of nasal irrigation. Laryngoscope. 2008;118:2078–81.
68. Wei CC, Adappa ND, Cohen NA. Use of topical nasal therapies in the management of chronic rhinosinusitis. Laryngoscope. 2013;123:2347–59.
69. Rudmik L, Smith TL. Evidence-based practice: postoperative care in endoscopic sinus surgery. Otolaryngol Clin North Am. 2012;45:1019–32.
70. Orlandi RR, Hwang PH. Perioperative care for advanced rhinology procedures. Otolaryngol Clin North Am. 2006;39:463–73, viii.
71. Wang DY, Wardani RS, Singh K, Thanaviratananich S, Vicente G, Xu G, et al. A survey on the management of acute rhinosinusitis among Asian physicians. Rhinology. 2011;49:264–71.
72. Lin SW, Wang YH, Lee MY, Ku MS, Sun HL, Lu KH, et al. Clinical spectrum of acute rhinosinusitis among atopic and nonatopic children in Taiwan. Int J Pediatr Otorhinolaryngol. 2012;76:70–5.
73. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54:e72–112.
74. Wald ER. Beginning antibiotics for acute rhinosinusitis and choosing the right treatment. Clin Rev Allergy Immunol. 2006;30:143–52.
75. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132:e262–80.
76. Kristo A, Uhari M, Luotonen J, Koivunen P, Ilkko E, Tapiainen T, et al. Paranasal sinus findings in children during respiratory infection evaluated with magnetic resonance imaging. Pediatrics. 2003;111:e586–9.
77. Marseglia GL, Pagella F, Klersy C, Barberi S, Licari A, Ciprandi G. The 10-day mark is a good way to diagnose not only acute rhinosinusitis but also adenoiditis, as confirmed by endoscopy. Int J Pediatr Otorhinolaryngol. 2007;71:581–3.
78. Falagas ME, Giannopoulou KP, Vardakas KZ, Dimopoulos G, Karageorgopoulos DE. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. Lancet Infect Dis. 2008;8:543–52.
79. Critchley IA, Jacobs MR, Brown SD, Traczewski MM, Tillotson GS, Janjic N. Prevalence of serotype 19A *Streptococcus pneumoniae* among isolates from U.S. children in 2005–2006 and activity of faropenem. Antimicrob Agents Chemother. 2008;52:2639–43.
80. Jacobs MR, Good CE, Windau AR, Bajaksouzian S, Biek D, Critchley IA, et al. Activity of ceftaroline against recent emerging serotypes of *Streptococcus pneumoniae* in the United States. Antimicrob Agents Chemother. 2010;54:2716–9.
81. American Academy of Pediatrics, Sub-committee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108:798–808.
82. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics. 1991;87:311–6.
83. Brook I, Gober AE. Antimicrobial resistance in the nasopharyngeal flora of children with acute maxillary sinusitis and maxillary sinusitis recurring after amoxicillin therapy. J Antimicrob Chemother. 2004;53:399–402.
84. Schaad UB. OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review. World J Pediatr. 2010;6:5–12.
85. Brook I. Bacteriology of acute and chronic ethmoid sinusitis. J Clin Microbiol. 2005;43:3479–80.
86. Muntz HR, Lusk RP. Bacteriology of the ethmoid bullae in children with chronic sinusitis. Arch Otolaryngol Head Neck Surg. 1991;117:179–81.
87. Hsin CH, Su MC, Tsao CH, Chuang CY, Liu CM. Bacteriology and antimicrobial susceptibility of pediatric chronic rhinosinusitis: a 6-year result of maxillary sinus punctures. Am J Ophthalmol. 2010;31:145–9.
88. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev. 2007:CD006394.
89. Ozturk F, Bakirtas A, Ileri F, Turktas I. Efficacy and tolerability of systemic methylprednisolone in children and adolescents with chronic rhinosinusitis: a double-blind, placebo-controlled randomized trial. J Allergy Clin Immunol. 2011;128:348–52.
90. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72:1541–5.
91. Criddle MW, Stinson A, Savliwala M, Coticchia J. Pediatric chronic rhinosinusitis: a retrospective review. Am J Ophthalmol. 2008;29:372–8.
92. Ramadan HH, Cost JL. Outcome of adenoidectomy versus adenoidectomy with maxillary sinus wash for chronic rhinosinusitis in children. Laryngoscope. 2008;118:871–3.
93. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. Ann Otol Rhinol Laryngol. 2010;119:578–82.
94. Hebert RL 2nd, Bent JP 3rd. Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. Laryngoscope. 1998;108:796–9.