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REVIEW ARTICLE

Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today?

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Abstract

State-of-the-art documents like ARIA and EPOS provide clinicians with evidence-based treatment algorithms for allergic rhinitis (AR) and chronic rhinosinusitis (CRS), respectively. The currently available medications can alleviate symptoms associated with AR and RS. In real life, a significant percentage of patients with AR and CRS continue to experience bothersome symptoms despite adequate treatment. This group with so-called severe chronic upper airway disease (SCUAD) represents a therapeutic challenge. The concept of control of disease has only recently been introduced in the field of AR and CRS. In case of poor control of symptoms despite guideline-directed pharmacotherapy, one needs to consider the presence of SCUAD but also treatment-related, diagnosis-related and/or patient-related factors. Treatment-related issues of uncontrolled upper airway disease are linked with the correct choice of treatment and route of administration, symptom-oriented treatment and the evaluation of the need for immunotherapy in allergic patients. The diagnosis of AR and CRS should be reconsidered in case of uncontrolled disease, excluding concomitant anatomic nasal deformities, global airway dysfunction and systemic diseases. Patient-related issues responsible for the lack of control in chronic upper airway inflammation are often but not always linked with adherence to the prescribed medication and education. This review is an initiative taken by the ENT section of the EAACI in conjunction with ARIA and EPOS experts who felt the need to provide a comprehensive overview of the current state of the art of control in upper airway inflammation and stressing the unmet needs in this domain.

Abbreviations
AB, antibiotics; AR, allergic rhinitis; AA, allergic asthma; ARS, acute rhinosinusitis; CRS, hronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; IT, immunotherapy; NP, nasal polyps; URTI, upper respiratory tract infection; SCUAD, severe chronic upper airway disease.

Chronic upper airway inflammation can roughly be divided into two major clinical entities, that is, rhinitis and rhinosinusitis. Among the different phenotypes of rhinitis, infectious and allergic rhinitis (AR) are those that are best characterized from a pathophysiologic point of view. Rhinitis is defined as a symptomatic inflammation of the nasal mucosa,

giving rise to at least two nasal symptoms being present for more than one hour per day (1). Allergic rhinitis requires the demonstration of IgE-mediated hypersensitivity using appropriate cutaneous or systemic tests (2). Chronic rhinosinusitis (CRS) is classically divided into a group with and without endoscopic or radiologic evidence of nasal polyps (CRSwNP and CRSsNP, respectively) (3). Both AR and CRS are characterized by inflammation, are divided into the mild, moderate and severe subgroups (1, 3, 4), and anti-inflammatory medication represents the first-line treatment. The treatment algorithms within ARIA (1, 5) and EPOS (3) documents provide evidence-based guidelines for treatment of AR and CRS. In AR, immunotherapy is advocated when pharmacotherapy is not successful. Surgical reduction of the inferior turbinate or surgical correction of a septal deviation is seldom indicated when nasal obstruction persists as a major symptom in adequately treated AR patients. Anti-inflammatory medication in combination with saline douching represents the first step of treatment for CRS, with adaptation of the therapeutic regimen dependent on whether symptom control is obtained (3). In CRS, surgery is considered if prolonged medical treatment fails.

Medical treatment for any condition aims at a total or clinically significant relief of symptoms. The degree of symptom reduction, the presence of adverse events and the outcome of treatment all determine control of the disease. In contrast to other diseases like asthma (6) and despite the high prevalence of AR and CRS (7, 8), the concept of control of disease has only recently been introduced in AR and rhinosinusitis. However, this concept is important to define that group of patients with difficult-to-treat disease, representing a diagnostic and therapeutic challenge and having a large socio-economic impact (9, 10). After defining those patients with uncontrolled disease, factors associated with lack of control can be identified and better addressed and better insight can be obtained in global airway disease control (11).

A recent retrospective analysis of patients with AR demonstrated that almost one-fifth of patients treated for AR do not respond satisfactorily to medical treatment (12), as their VAS scores for nasal symptoms remained higher or equal to 5 with associated persistent severe ocular symptoms. As a consequence, the lack of control by medical treatment was proposed by Bousquet et al. (12) as a VAS score for total nasal symptoms of 5 or more after treatment and/or severe ocular symptoms.

Difficult-to-treat rhinosinusitis has been proposed as a separate clinical entity in those patients with CRS experiencing insufficient symptom control despite adequate medical and surgical therapy (3). It is estimated that up to 20% of CRS patients are not well controlled by guideline-based treatment. The third EPOS contains the first proposal for defining the concept of control in rhinosinusitis (3). Based on a combined evaluation of symptom severity, mucosal aspect and need for systemic medication, CRS patients are defined as controlled, partly controlled or uncontrolled (Table 1). The concept of control in AR and CRS opens new venues for research, primarily aiming at unravelling underlying mechanisms responsible for the lack of control. After defining those patients with uncontrolled disease, factors associated with lack of control can be identified and better addressed.

This review is an initiative taken by the ENT section of the EAACI in conjunction with ARIA and EPOS experts who felt the need to provide a comprehensive overview of the current state of the art of control in upper airway inflammation, as these concepts are becoming more important. The current state of the art on control of upper airway disease will be reviewed in parallel with highlighting the different factors involved in uncontrolled upper airway inflammation (Fig. 1) and highlighting the unmet needs in this domain.

Defining control in AR and CRS

In general, the goal of treatment for any medical condition is to achieve and maintain clinical control. Control is defined as a disease state in which the patients do not have symptoms anymore or the remaining symptoms are not regarded as

Table 1 Proposed criteria for defining controlled, partly controlled and uncontrolled chronic rhinosinusitis (CRS), taken from the 2012 update of the EPOS document (with permission of Rhinology)

	Controlled	Partly controlled	Uncontrolled
Assessment during the last month	All of the following	At least one feature present	Three or more features of partly controlled CRS
Nasal blockage	Not present or Not bothersome	Present on most days of the week	
Rhinorrhoea/post-nasal drip	Little and mucous	Mucopurulent on most days of the week	
Facial pain/headache	Not present or Not bothersome	Present	
Smell	Normal or slightly impaired	Impaired	
Sleep disturbance or fatigue	Not impaired	Impaired	
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa (nasal polyps, mucopurulent secretions, inflamed mucosa)	
Systemic medication needed to control disease	No needed during the last 3 months	Need of a course of AB or systemic CS in the last 3 months	Need of long-term AB or systemic CS in the last month

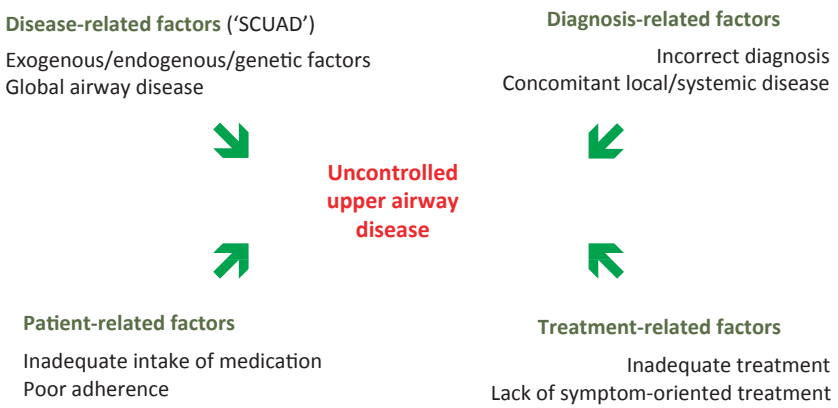

Figure 1 Different factors related to uncontrolled upper airway disease. Disease-related, diagnosis-related, treatment-related and therapy-related factors all need to be considered in failure to control allergic rhinitis (AR) and chronic rhinosinusitis (CRS).

bothersome. In AR and CRS, symptoms are a consequence of the inflammatory reaction within the mucosa, and control of symptoms is primarily achieved by anti-inflammatory treatment regimens. So far, the concept of control is not well defeated in AR and CRS.

In AR, Bousquet et al. (12) proposed a simple VAS score as clinical tool for evaluation of control, with a VAS score for total nasal symptoms of 5 or greater as the cut-off point for uncontrolled disease. Based on a retrospective analysis, it was estimated that one-fifth of patients with AR are uncontrolled despite adequate medical treatment of AR (12). Of note, treatment of AR according to the ARIA guidelines was associated with a lower incidence of uncontrolled rhinitis (10%) than free-choice anti-allergic (18%) treatment. Interestingly, the use of a VAS score for total nasal symptoms turned out to be a convenient tool for evaluation of control in AR as it embedded information on a validated rhinitis quality-of-life questionnaire and the reflective total nasal symptoms scores (RT4SS).

For rhinosinusitis, a more complex concept of control has recently been proposed in the 2012 update of the EPOS document (Table 1) (3). For the sake of uniformity and taking into account the concept of global airway disease, the proposal of disease control in rhinosinusitis was similar to the tool for evaluation of asthma control in the GINA guidelines (13). A combined evaluation of the severity of sinonasal symptoms by the patients, clinical evaluation of the mucosa and need for systemic treatment over the course of the last month are taken into account for defining a patient as being controlled, partly controlled or uncontrolled (Table 1).

Following the treatment algorithms of ARIA and EPOS, the therapeutic effect of a recommended treatment needs to be evaluated after 2–4 weeks for AR and after 3 months for CRS. At present, time-related issues for evaluation of control are proposed to be 2 weeks of treatment for AR (3) and the last month of therapy for CRS (3). Following the evaluation of control, treatment is adapted according to ARIA (Fig. 2) and EPOS (Fig. 3) guidelines, respectively.

Disease-related factors in uncontrolled upper airway symptoms

The concept of severe chronic upper airway disease has been introduced to define those patients with severe and uncontrolled disease despite guideline-based treatment, which thus represents a therapeutic challenge (14).

In fact, patients with severe AR may not respond sufficiently to adequate medical treatment. Several factors may be responsible for this severe phenotype of AR in a subgroup of individuals that do not respond well to medication (15). Environmental factors like allergen load, exposure to cigarette smoke, indoor and outdoor pollutants, and occupational factors may contribute to the severity and persistent nature of allergic airway symptoms in AR patients (15). Among hormonal factors, female sex hormones have been associated with more severe allergic inflammation (1). As a rule, one-third of patients experience more symptoms related to allergy during pregnancy than beforehand. Genetic factors are involved in the inflammatory response and may determine the balance between pro-inflammatory and anti-inflammatory protein secretion (16) as well as the presence of mucosal hyperreactivity (17). For unknown reasons, neuroinflammatory mechanisms may in some patients with AR be more prominent than in others, giving rise to sneezing and itchy nose. Mediators like substance P have been associated with different symptoms in patients with AR(18) as well as in nonallergic, noninfectious rhinitis (19). Similar to asthma, steroid resistance has been reported in AR (20) and CRS (21) and may be a reason for lack of control in both conditions. The mechanisms of steroid resistance in AR and CRS are far from being validated (22).

Chronic rhinosinusitis represents a multi-factorial disease with anatomic, humoral, environmental, endogenous and even iatrogenic factors being involved in the pathophysiology (3). In individual patients with CRS, it is often difficult to pinpoint the contribution of these individual factors to the chronic sinonasal inflammation, and the role of microorganisms is not always clear (23). However, it is important to

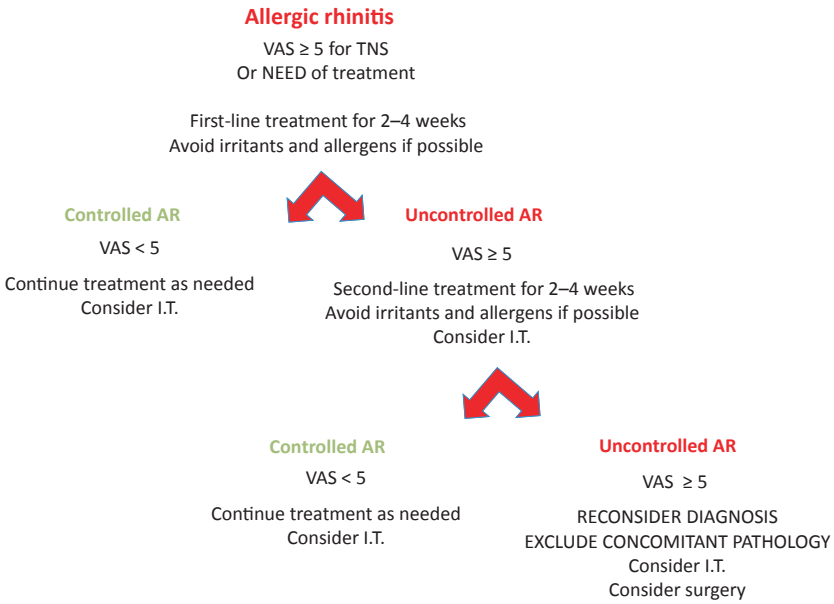

Figure 2 Treatment algorithm for AR in relation to control, adapted from the ARIA guidelines (1).

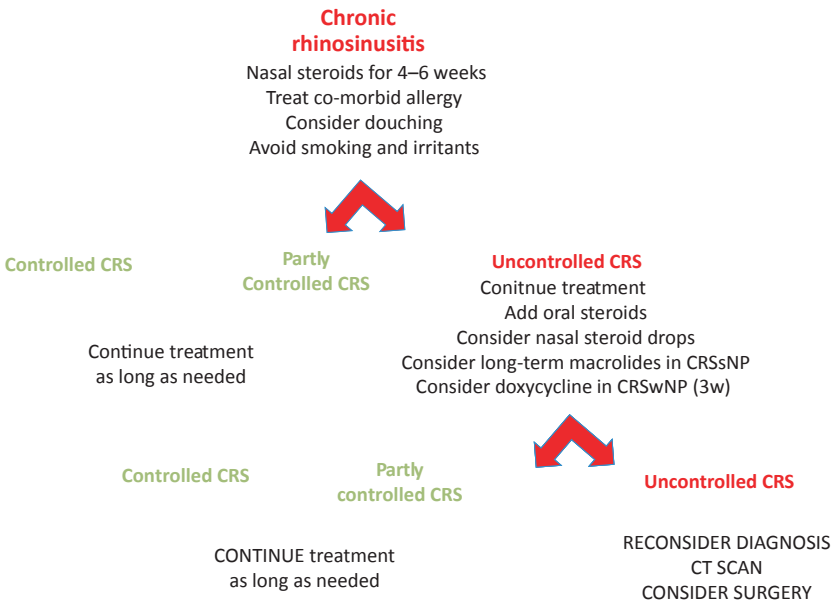

Figure 3 Treatment algorithm for CRS in relation to the recently proposed terminology of disease control, with proposed treatments adapted from the treatment algorithms of EPOS update 2012 (3).

acknowledge the fact that each of these factors may act in concert to induce sinonasal inflammation. Like in AR, similar environmental and hormonal factors may aggravate sinonasal inflammation. In addition, immune deficiencies, mucociliary dysfunction and cystic fibrosis may underlie uncontrolled CRS (3). CRS is often found in asthma and COPD patients (24), with more recurrent disease after surgery in the asthma patients than in nonasthma patients (25). Within the CRS group, patients with NP represent a group with a typical inflammatory profile, with aspirin-intolerant patients presenting with the most severe form of CRSwNP (3).

Diagnosis-related factors of uncontrolled upper airway symptoms

In uncontrolled upper airway disease, one needs to reconsider the diagnosis of AR and/or CRS at a certain stage (Fig. 2 and 3), in an attempt to find out whether any other factors

have been overlooked or even an incorrect diagnosis is responsible for the lack of control. Different AR (26) and CRS (3) phenotypes have been recognized.

The diagnosis of AR needs to combine symptoms suggestive of AR and the demonstration of an allergic sensitization (e.g. positive skin prick testing or serum-specific IgE). In a subgroup of AR patients, nasal hyperreactivity (NHR) represents a major presenting symptom that is often not adequately addressed. Apart from the history for diagnosis, NHR can be objectively measured using different provocation techniques among which the challenge with cold dry air represents a useful tool (27), which is superior to histamine challenge (28). In addition to the inflammatory aspects of AR, several factors may aggravate the degree of nasal obstruction and nasal secretions in patients with AR (29). It is likely that nasal congestion in AR patients with septal deviation, nasal valve dysfunction and/or presence of NP has a larger impact on the symptoms in these patients compared with AR patients without functional pathology or NP (30). Nasal obstruction, secretions or rhinorrhoea become more bothersome in those children with AR and adenoid hypertrophy, than in those without blockage of the nasopharyngeal cavity by enlarged adenoids (29). A skull base defect with leakage of cerebrospinal fluid should be excluded preferably by measuring β2 transferrin or β trace in the nasal secretions (31) in those patients with rhinitis with significant watery rhinorrhoea insufficiently controlled by medical treatment. In children with rhinitis and nasal obstruction, adenoid hypertrophy as well as choanal atresia should not be overlooked (29).

In severe CRS, impaired mucociliary drainage, immune deficiencies and/or iatrogenic factors need to be recognized as reasons for failure of treatment (32). Ganulomatous diseases like Wegeners' disease or sarcoidosis should be considered in those patients with general malaise and nasal crusting. In patients with severe CRSwNP, the presence of aspirin intolerance, asthma, COPD, bronchiectasis, Church Strauss syndrome, cystic fibrosis and primary ciliary dyskinesia have all been shown to be negative predictors of outcome of treatment (3). The diagnosis of these conditions should be considered in case of uncontrolled disease using the recommended diagnostic tools (2), as these diagnoses are often associated with the perspective of changing the treatment strategy towards a more appropriate treatment and better information to the patient.

Treatment-related factors of uncontrolled upper airway symptoms

Optimal treatment for AR and CRS involves the best choice of treatment by the physician, with careful evaluation of the need for pharmacotherapy or association of pharmacotherapy and immunotherapy based on the severity and type of symptoms. Ideally, the expected therapeutic effects of different treatment options including immunotherapy are taken into account. Indeed, different types of molecules have different therapeutic profiles on a variety of symptoms with some molecules having a wider therapeutic range and/or more specific action on certain symptoms than others (1). The route and dose of administration of pharmacotherapy also has an impact on the therapeutic effects (33). In AR patients, sufficient attention needs to be paid to ocular symptoms and appropriate nasal and ocular treatment (34). Treatment-related factors in uncontrolled CRS have not been well characterized but can roughly be divided into inappropriate medical treatment or inappropriate/incomplete surgery. Treatment may not be adequate in those CRS patients in whom nasal anti-inflammatory treatment cannot be taken due to local or systemic adverse events, where douching is not supported and/or long-term macrolides are not tolerated. Depending on the underlying aetiology, it is estimated that up to 85% of patients undergoing endoscopic sinus surgery (ESS) benefit from the intervention (35), with a significant reduction in symptom severity or total cure. Besides surgical skills, several factors like smoking, occupational factors, allergy, asthma and aspirin intolerance negatively affect the outcome after ESS (35, 36).

Patient-related factors of uncontrolled upper airway symptoms

The first questions one should ask when dealing with uncontrolled AR relates to the patient's compliance in correct medication use and adherence to the prescribed therapy.

Concerning nasal treatment, the proper technique for nasal drug delivery is believed to be a major issue in the efficacy and induction of adverse events related to prolonged use of nasal sprays. In spite of the lack of solid data, it seems logic that inappropriate use of intranasal spray without blowing of the nose prior to application of the spray, bad positioning of the nasal spray at the time of nebulization of the molecule and/or nasal expiration rather than breath holding or inspiration at the time of nebulization may be responsible for suboptimal effects of the intranasal treatment.

Correct utilization of the prescribed medication may not be a major issue in short-term treatment but represents a key factor for obtaining control by medical treatment beyond several weeks (37). In accordance with studies in other medical fields, adherence to the prescribed treatment like immunotherapy is found to be as low as 50% after 1 year of treatment (38). Also in CRS patients undergoing sinus surgery, a recent survey showed that only 43% correctly used the prescribed nasal drugs (39).

Among subjective factors that are estimated to be important in adherence, prejudices about treatment, fear of adverse events and economic reasons are considered key factors in determining whether a patient will take the prescribed medication (38, 40). Patients' perceptions of the treatment are considered responsible for under-treatment of AR in Europe (41). A recent survey performed among rhinitis patients undergoing skin prick testing for demonstration of sensitization, revealed that up to 50% of patients feared adverse events of the medication prescribed for AR (42). As a consequence, medical doctors may need to discuss these issues with the patient to obtain the best possible adherence to treatment. Also patients' expectations of

prescribed treatment for AR may interfere with utilization, as it is unlikely that symptomatic treatment will be taken if cure from disease is the patient's goal. A recent survey demonstrated that up to 40% of patient with a new diagnosis of AR want to be cured from their allergy besides symptomatic relief (42). Finally, the different treatment options for AR or CRS all have reported adverse events in a minority of patients, which may be responsible for so-called drug holidays or lack of compliance. A large amount of work still needs to be performed on compliance in the medical treatment of AR and CRS.

Unmet needs in uncontrolled AR

- Validation of the VAS scoring system as a clinical tool for evaluation of control in AR, involving short-term and long-term evaluation of symptom control in AR.
- Evaluation of diagnostic, therapeutic and patient-related factors responsible for uncontrolled AR.
- Defining success of medical treatment including immunotherapy in terms of control in AR.

Unmet needs in uncontrolled CRS

- Validation of the proposed definition of control for CRS.
- Evaluation of the prevalence and pathophysiology of uncontrolled CRS in clinical practice.
- Development of a strategic diagnostic and therapeutic plan following disease control in CRS.

Conclusion

Currently available treatment regimens for AR and RS are effective in the majority of patients suffering from AR and CRS. Both short- and long-term symptom controls remain the primary aims of treatment. Control in AR is based on a VAS scoring system for total nasal symptoms, whereas a more complex evaluation is proposed for CRS. The novel concepts of control of AR and CRS allow the clinician to define those patients that represent a therapeutic challenge. Obtaining better insight into the different factors responsible for the lack of symptom control is warranted to obtain improved symptom control in both rhinitis and rhinosinusitis.

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