



Short review

Pediatric rhinosinusitis and asthma

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ABSTRACT

Both asthma and rhinosinusitis are complex and heterogeneous diseases and, importantly, they often coexist: these diseases can be concomitant in 35–65% of affected children, according to different studies. Thus, evaluating this comorbidity in the clinical practice should be paramount. In this review, we focused our discussion on the multiple pathophysiological aspects that may link rhinosinusitis and asthma in the pediatric population. Although rhinosinusitis may exacerbate asthma through several mechanisms occurring by contiguity, actually this aspect seems to be only one component of the complex interplay between upper and lower airways. In particular, the onset of an important and persistent Th2-driven inflammatory process dominated by eosinophils presence at one site of the airways, may release into the bloodstream several cytokines; in their turn, those can lead to the stimulation of the bone marrow, which may function as a systemic amplifier of such an eosinophilic inflammation.

1. Introduction

Sinusitis generally refers to the inflammation in the nasal sinuses and, as it is usually associated with the inflammation of nasal mucosa (namely, rhinitis), the term rhinosinusitis (RS) is currently considered to be more appropriate [1].

It is important to underline that RS is not exclusively a disease of adulthood: indeed, RS must be suspected in both pediatric and adult patients complaining of nasal symptoms, such as nasal congestion and/or rhinorrhea, persisting for more than 7–10 days without any improvement. Such a temporal cut-off is useful to distinguish RS from self-limiting upper respiratory infections (URIs), caused by viral agents: these latter clinical conditions can show the same pattern of symptoms, but usually resolve by 7–10 days [3–5]. By definition, the symptoms of acute RS (ARS) resolves within 3–4 weeks; if sinus inflammation persists (regardless of the medical management), it could evolve to chronic RS (CRS), defined by a disease duration longer than 8–12 weeks [1,2].

Therefore, the diagnosis of RS often relies on clinical findings only, including the duration of nasal symptoms, the characteristics of nasal discharge (e.g. purulent) and the presence of other manifestations, such as facial pain and fever. Computerized tomography (CT) is required whenever the suspicion of extra-sinus complications should arise [6–9]. Moreover, in patients with CRS, CT can also permit the detection of nasal polyps in the sinus cavities, as nasal endoscopy can identify those protruding in the nasal cavities. According to the endoscopic and/or

radiological findings, there are CRS forms without nasal polyposis (CRSsNP) and others with nasal polyposis (CRSwNP). Epidemiological evidences suggested that CRS is especially prevalent among patients with asthma, in addition to patients with immunodeficiency, cystic fibrosis and aspirin allergy [9–11].

In this review, we will discuss the complex relationship linking RS and asthma in children. We aim at providing a comprehensive overview on the current evidences deriving from pediatric studies and, then, at analyzing those in light of the interplay among the multiple immunopathological aspects that may be implicated.

2. Epidemiological aspects

Although the respiratory system has been traditionally divided into upper and lower tracts, actually many patients complaining of respiratory diseases often show an extensive involvement of both sections. For instance, rhinitis and asthma frequently coexist. As regards RS, a number of studies have evidenced its association with asthma since 1920s; importantly, several studies suggested the importance of RS in triggering and/or worsening asthma in both adults and children [12,13].

Recently, the study by Matsuno et al. reported the prevalence of RS diagnosis in the general asthmatic population, as being 36.7%. Interestingly, sinus CT abnormalities were detected in 66.3% of patients with asthma: although these CT findings were reported much more

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frequently in patients with moderate to severe asthma, actually also some patients with intermittent or mild persistent asthma were found to have concomitant sinus inflammation. In general, patients with severe and persistent asthma were 14.3% among those diagnosed with RS, whereas such a percentage decreased to 3.8% in patients without RS [14]. Previously, other studies evidenced the frequent occurrence of CRS in adult patients with severe and steroid-dependent asthma. In particular, Crater et al. estimated the prevalence of RS in asthmatic patients as comprised between 35% and 45%; additionally, mucosal thickening in sphenoid, ethmoid, and frontal sinuses was significantly more common in asthmatic patients than in controls, represented by people evaluated for non-respiratory diseases [15–18]. Unfortunately, here it was not possible comparing the prevalence of sinus abnormalities between asthmatic patients and those with isolated URIs.

Similar findings have been reported in the pediatric population. However, the number of pediatric studies is much fewer than for asthmatic adults. Recently, our group described 294 consecutive asthmatic children (mean age, 7.3 years) investigated by nasal endoscopy: occult sinus involvement was demonstrated in 7.5% of cases, who resulted to have poorly controlled asthma [19]. Actually, the comorbidity between RS and asthma in children has been noticed for several decades. In 1994, Fuller et al. demonstrated that 27% of children admitted to the hospital with severe asthma had abnormal findings on sinus radiograph [20]. One more recent study by Tosca et al. showed that about 50% of children diagnosed with persistent asthma presented concomitant RS by nasal endoscopy [21].

Therefore, the association between RS and asthma seems to be quite clear: especially children and adolescents affected by poorly controlled asthma should be investigated for occult or manifest RS by nasal endoscopy and, eventually, by CT, if appropriate. However, it is still debated whether such an association is due to a causal relationship, meaning that RS is part of the etiology of asthma, or actually asthma and RS are different pathological and clinical manifestations of the same underlying disease process, according to the so-called United Airways Disease concept [22].

3. Rhinosinusitis as a causative factor of asthma

The main argument supporting the role of RS - and CRS in particular -, as a co-causal or worsening factor of asthma is the improvement of its control after the resolution of sinus disease, through the appropriate medical therapy or surgery (e.g. functional endoscopic sinus surgery, FESS), if needed [2,23].

Back to 1984, Rachelefsky et al. showed that 79% of children (aged 4–13 years) with poorly controlled asthma were able to discontinue bronchodilators after the medical treatment of CRS: moreover, 67% of children normalized their pulmonary function tests, too [24]. Similar findings were reported in a set of smaller studies, where most children receiving medical treatment for concomitant RS improved their asthma control [21,25–27]. Oliveira et al. reported that children affected with RS improved their bronchial hyper-responsiveness to methacholine, and decreased their asthma symptoms after the medical treatment of RS [28]. The prospective study by Tsao et al. including 41 children medically treated for CRS, showed an increase of the provocative concentration of methacholine causing 20% fall in FEV₁, compared to pre-treatment values. Again, children undergoing surgical management for CRS showed an improvement of their lower airway disease [29]. In the study by Parsons et al. including 52 pediatric patients, there was a 96% decrease in asthma symptoms assessed by a retrospective interview, in addition to the significant reduction of monthly asthma exacerbations and of emergency room visits, after the surgical management of CRS [30]. In the study by Manning et al. including 14 steroid-dependent children with asthma and CRS, most of them showed improvement in their asthma control after FESS [31].

Thus, a number of clinical evidences suggested that CRS influences the course and/or the occurrence of asthma. Several mechanisms may

explain this relationship: i) nose-pharynx-bronchial reflexes; ii) post-nasal drip with drainage of inflammatory mediators into the lower airways; iii) inhalation of polluted and/or cold and/or dry air into the lower airways [32].

Nose-pharynx-bronchial reflexes in human and animal models can occur after nasal stimulation with a variety of substances and physical agents. The stimulation of receptors in the nose, pharynx and also in sinuses may generate nervous signals transmitted to the central nervous system, through afferent fibers of the trigeminal nerve; such a signal may be elaborated in the brainstem in order to generate a reflex efferent signal via the parasympathetic nervous system, affecting bronchial muscle tone and, ultimately, inducing lower airways constriction [12,33]. Rolla et al. showed that the damage of the pharyngeal mucosa in patients with CRS (mediated by the drainage of inflammatory mediators and cells and/or of infected material, probably) increased the exposure of sub-mucosal nerve to irritants, leading to the activation of the reflex arc [34].

As for the post-nasal drip, it could not be limited to the pharynx and its effects might extend to lower airways directly; however, those few available studies have not clearly supported this hypothesis. Indeed, Bardin et al. showed that there was no pulmonary aspiration of sinus content in patients with concomitant asthma and RS, through a study carried out by the placement of radionuclide into the sinuses [35]. Actually, through a similar study approach, Ozcan et al. reported some degree of pulmonary aspiration of radionuclide-labelled nasal secretions during sleep, but the difference between patients with comorbid asthma and sinusitis, and the healthy patients recruited as a control group, was not significant [36].

Finally, the possibility that the loss of function of inflamed/infected sinuses may result in the impairment of air modifications is quite intriguing, in light of some recent evidences. Abnormal breathing (excluding the passage of air throughout the sinus system) impairs air warming, humidification and purification from pollutants and irritants: that may allow physical factors and chemical agents to act on the lower airways [37]. Moreover, in allergic patients, the impairment of air filtering in presence of sinus disease might also increase the allergen load reaching the bronchial system. Actually, research studies testing primarily this hypothesis are not available, yet. However, Papp et al. compared the nasal-air conditioning between patients with CRSwNP (before and after sinus surgery) and healthy control subjects: the nasal heat increase and humidification was significantly lower before surgery in patients compared to controls. Interestingly, patients showed a significant improvement in the heating capacity of the nasal airways 4–6 weeks after surgery, but there was no significant improvements in nasal humidification [38].

4. Inflammation in asthma and CRS

Infectious-related and/or immune-mediated inflammatory mechanisms may be variably implicated in the etiology and pathogenesis of CRS.

Whereas in ARS infections – probably the superimposition of bacterial infections on a preceding viral illness – represent the main causative factor, in CRS a primitive non-infectious inflammatory mechanism may provide the pathological basis, where super-imposed infections may contribute to the perpetuation of the chronic inflammation. Impaired epithelial functioning, altered innate and adaptive immunological interplay with environmental agents (including microorganisms and pollutants), and tissue re-modelling may be all contributive factors to the development of CRS. A recent large population study showed a familial risk in children with CRS. Another study suggested a role for two airway epithelial potassium channels as susceptibility loci for CRS; anyway, it is known that children with immunologic disorders, ciliary dyskinesia and cystic fibrosis are predisposed to suffer CRS [39–41]. Importantly, antibody deficiency is an important immunologic factor contributing to a continuous

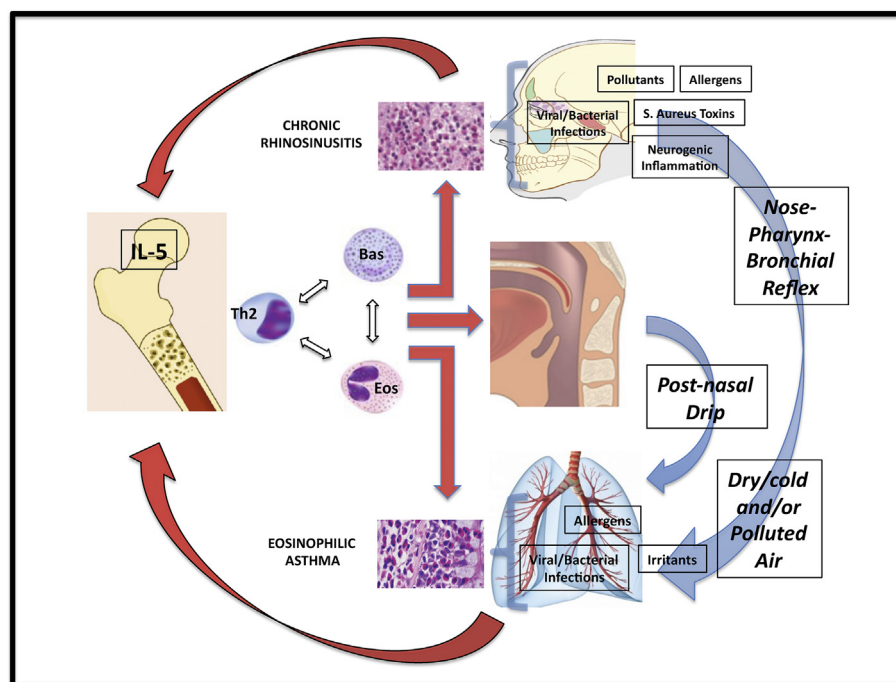


Fig. 1. Overview on the complex interplay between immunological and local mechanisms in patients with asthma and rhinosinusitis, according to the United Airway Disease theory.

inflammatory response in both upper and lower airways [42].

However, despite the potential heterogeneity of the etiological background, the presence of prevalent eosinophilic infiltration of the inflamed mucosa was found to be the most constant pathological finding in CRS; importantly, this feature was equally observed both in allergic and non-allergic patients. Such a pathological finding might be due to a prevalent Th2 immune response, and a similar pattern of cytokines, including an increased production of IL-4 and TNF- α , has been described regardless of a recognizable IgE-mediated environmental sensitization or allergy. The eosinophils in the sinus mucosa are supposed to be the main responsible of the initial tissue damage: an alteration in epithelial innate immunity and/or a maladaptive Th2 response have been noticed in patients with CRS, especially in those with nasal polyps [43,44]. In turns, these aspects may promote the bacterial aggression of sinus mucosa: in particular, *Staphylococcus aureus* can provide super-antigenic stimulation to the adaptive immune system, through the production of exotoxins, and its biofilms have been associated with eosinophilic inflammation, elevated eosinophilic cationic protein and IL-5 levels [45,46].

Compared to CRS, the inflammatory phenotype of asthma is more heterogeneous, although Th2 response is commonly implicated. In asthma, the eosinophilic inflammation of bronchial mucosa is mainly consistent with an allergic background. The classical asthmatic phenotype of the allergic patient shows eosinophilia and concomitant high circulating total and/or specific IgE levels [47]. This eosinophilic phenotype of asthma is prominently associated with CRS. Mehta et al. conducted an observational study including 201 patients with asthma undergoing sinus CT: it revealed sinus disease in 68% of their cohort and, interestingly, a severe mucosal thickening was associated with higher eosinophil levels in blood and sputum; moreover, patients with more severe sinus disease showed a statistical trend toward lower values of mean FEV1 than others [48]. Furthermore, Ponikau et al. examined the pathological specimens from 22 randomly selected patients with refractory CRS undergoing endoscopic sinus surgery. Importantly, 15 of 22 (68%) of the patients with CRS had been previously diagnosed with asthma, and the remaining patients with CRS showed bronchial hyper-reactivity through methacholine challenge test. The specimens

from all patients with CRS revealed epithelial damage (shedding) and basement membrane thickening with heterogeneous eosinophilic inflammation, which did not differ between allergic and non-allergic patients [49].

5. Rhinosinusitis and asthma: United Airways Disease

Several pathological findings and clinical observations suggested that CRS and asthma may be part of the same disease process, characterized with eosinophilic inflammation involving diffusely the respiratory airways, from the nostrils to the bronchi, which constitutes the pathological basis of the so-called “United Airways Disease” theory. According to this concept, respiratory inflammation may start at one site and extend to other sections eventually, and vice versa; the link between upper and lower airways disease may be a systemic inflammatory and immunological response passing through the bone marrow and, thus, not only an extension of the inflammation by contiguity [50].

After allergen exposure, basophils and eosinophils have been demonstrated to rise in the circulation and airway tissues, because of the release from storage pools in the bone marrow and their migration in peripheral tissues providing the appropriate homing signals [32]. Previously, our group showed that basophils and Th2 lymphocytes significantly increased at several sites, including spleen and bronchial airways, upon simple intra-nasal allergenic exposure, through an experimental murine model of eosinophilic asthma triggered by *Aspergillus fumigatus* sensitization [51–53].

Briefly, according to the current theory of the United Airway Disease, triggering allergic or non-allergic eosinophilic inflammation in the airways may stimulate the bone marrow to produce inflammatory cells and mediators, which have effects upon other respiratory sites than those affected initially. Therefore, the coexistence of pediatric RS and asthma may result from the complex interplay among several immunological mechanisms, which take place both inside and outside the respiratory system. Current evidences supported the occurrence of a systemic immune and inflammatory response (upon respiratory exposure to allergen and/or other irritant agents), by which immune cells

and mediators are released from the bone marrow and other lymphoid organs, reinforcing the inflammatory process in the airways and extending it beyond the original site. However, local mechanisms, such as nose-pharynx-bronchial reflexes, post-nasal drip and inhalation of polluted and/or cold air may further exacerbate the inflammatory disease from upper to lower airways, but they are not the main determinants. Indeed, asthma can anticipate the development of pediatric RS, which, in turn, may affect the lower airways inflammation. A schematic representation of all the factors supposed to interplay in the United Airways Disease theory is provided in Fig 1.

Anfuso et al. showed that the inflammatory response in the sinus and adenoid tissues of children with CRS is qualitatively similar - but quantitatively amplified - if there is a concomitant diagnosis of asthma. Specifically, the cytokines and chemokines that were significantly increased in the CRS-only group (with no asthma and/or allergic rhinitis), compared to the control group, resulted to be expressed at higher levels in the asthmatic patients with CRS [54].

Recently, Tan et al. investigated the pre-existing pathological conditions in patients of all ages diagnosed with CRS. They found a variable - but statistically significant - association between several diseases of the upper airways (e.g. chronic rhinitis, acute sinusitis, otitis media, adenitis/tonsillitis) and lower airways diseases (e.g. bronchitis, asthma, pneumonia), as pre-morbid conditions in patients (adults and children) with a subsequent diagnosis of CRSsNP. Similar associations were described for patients with CRSwNP, but these results achieved no statistical significance, possibly because of the smaller size of the CRSwNP study group. These findings could support the Unified Airway Disease concept. Importantly, among lower airways diseases, asthma resulted to be the clinical condition showing the strongest association with CRS: in particular, the adjusted odds ratio (aOR) related to asthma, as a pre-morbid condition of CRSwNP and CRSsNP, was 3.2 and 1.8, respectively. These results were even more evident considering a narrower time window (0–6 months before the diagnosis of CRS): here, the aOR reached the values of 4.4 and 2.5, respectively. Hence, this study suggested that asthma could precede CRS in some patients and this occurrence is prevalently associated to CRSwNP [55].

More recently, the same researchers approached this issue also from the other temporal side: they evaluated the risk of incident diseases within 5 years after a new diagnosis of CRS, considering both CRSwNP and CRSsNP, separately. Through a case-control study, they confirmed that patients with CRS (both CRSsNP and CRSwNP) are at increased risk to develop other respiratory diseases [56]. However, their results also suggested different temporal patterns of incident diseases between these two forms of CRS: indeed, asthma was confirmed to preferentially precede the onset of CRSwNP, whereas asthma appeared to equally precede or follow the diagnosis of CRSsNP.

Thus, these two phenotypes of CRS, namely CRSwNP and CRSsNP, may be the expression of the different progression and/or severity of the same disease, but this concept has not been ascertained yet. It is estimated that 7% of asthma patients are diagnosed with nasal polyps; in non-atopic asthma and late-onset asthma, polyps are diagnosed more frequently (10%–15%). Finally, nasal polyps are a common pathological feature of aspirin-induced asthma, which has an estimated prevalence of 1% in the general population and 10% among asthmatics [57]. Basically, nasal polyps represent a form of chronic inflammation affecting the mucosa of ethmoid sinus cavities of some susceptible individuals, probably. Although a large heterogeneity exists between inflammatory polyps, those usually showed some common features, such as thickened basement membrane and edematous-to-fibrotic stromal tissue, with a reduced number of vessels and glands, and no neural structures. Among the inflammatory cells, eosinophils resulted the prominent cell type in about 80% of nasal polyps: these cells localize around the vessels, glands, and directly beneath the mucosal epithelium.

Activated eosinophils are common in biopsies taken from the sinuses of allergic and non-allergic patients. Among patients with

untreated CRS, those with CRSsNP have fewer eosinophils (2% of cells, on average) than those with CRSwNP (around 50% of inflammatory cells) [58]. This finding suggested major differences in the pathophysiology of the two forms of CRS. It is likely that the mucosal eosinophilia in nasal polyps may be due to a self-sustaining mechanism, through the local release of inflammatory mediators, probably because of the super-imposition of additional factors during the course of CRS. Thus, CRSwNP might represent a different and/or later point of the “disease march” of CRS. However, the different immune responsiveness of the individual might be implicated, too [59].

Several evidences suggested that airborne or local microorganisms induce or aggravate the inflammation seen in CRS. Biofilms aggregate and protect bacteria on mucosal surfaces within a matrix of polysaccharides, nucleic acids, and proteins, promoting persistent inflammation and decreasing the efficacy of antimicrobials and the host defenses [2,60]. Recently, an increased colonization with *S. aureus* and the presence of specific IgE directed against *S. aureus* enterotoxins (SAEs) were described in nasal polyp tissue of patients with CRSwNP. Interestingly, the rates of colonization and tissue IgE were increased in subjects with co-morbid asthma or aspirin sensitivity [61]. By super-antigenic activity, SAEs may activate inflammatory cells in an antigen-unspecific way [62]. This mechanism could fit with the pathogenesis of nasal polyps in cystic fibrosis, too. Here, in addition to *P. Aeruginosa*, the most common pathogen colonizing the airways is *S. aureus* [63]. Moreover, Ponikau et al. suggested also a potential role for fungi, especially *Alternaria* spp., in the generation of nasal polyps [64]. Similarly, Cimmino et al. described the allergic sensitization to *Aspergillus fumigatus* in some patients with CRSwNP [65]. However, these latter agents resulted to be involved in a minority of cases.

In the perspective of the United Airways Disease theory, Hellings et al. provided a crucial observation: they reported that the nasal application of SAEs was able to aggravate an experimental model of allergic rhinitis and asthma, with a parallel increase of bronchial and systemic Th2 cytokines, such as IL-4, IL-5 and IL-13. Cytokines such as Eotaxin, IL-5, and RANTES provided the signal for the chemotaxis coordinating the movement of eosinophils into the inflamed respiratory tissues [50,66]. Indeed, the histological features of CRS and comorbid asthma largely overlapped: both sinus and bronchial mucosa showed eosinophilic inflammation and signs of airway remodeling [49].

CRS and asthma may interplay also via the systemic route, through the release in the blood of pro-inflammatory cytokines, including IL-5, from the peripheral sites; then, those mediators act on the bone marrow, leading to the maturation and the mobilization of inflammatory cells, including eosinophils and basophils [67]. In a study involving non-asthmatic patients with seasonal allergic rhinitis, inhaled allergen challenge elicited also an increase of IL-5 in the plasma [68]. Increased levels of IL-5-responsive CD34⁺ cells have been found in the bone marrow and in the peripheral blood of atopic individuals with allergic disorders, including nasal polyposis and asthma [69]. However, the specific mediators leading to this up-regulation of IL-5Rα on CD34⁺ progenitors *in vivo*, have not established. Some evidences pinpointed IL-5 itself as a potential regulator of IL-5Rα expression on bone marrow progenitors.

Then, eosinophils and progenitors released from the bone marrow can reach the airways, including those sections where the inflammatory process had not arisen primitively [67]. Interestingly, the number of IL-5-producing T cells in the bone marrow increased after inhalation challenge with allergens [70]. Moreover, the transfer of allergic disease into non-allergic individuals could occur after bone marrow transplantation [71].

Therefore, eosinophils infiltration may spread throughout the airways, probably in a lesser extent than in the site of primary inflammation. Such a process could be as more expressed as the eosinophilic inflammation in the original site is greater. By instance, CRSwNP is more commonly associated with lower tract respiratory disorders, such as asthma and nonspecific bronchial hyper-reactivity [72]. As

described, the eosinophil reaction in the sinuses is greater in presence of nasal polyps; SAEs, inducing local polyclonal IgE production, may promote eosinophilic inflammation in nasal polyposis [73]. In such a pathological setting, the eosinophilic inflammation was significantly more severe in terms of synthesis of IL-5 and other inflammatory mediators, and most patients resulted to have asthma and aspirin hypersensitivity, too [59]. Some authors reported that, in patients with CRSwNP, asymptomatic bronchial hyper-reactivity and asthma were associated to eosinophilic bronchial inflammation, which was not so pronounced in patients with nasal polyps, but no bronchial hyper-reactivity [74].

6. Conclusion

The epidemiological association between RS (especially, if chronic) and asthma has been clearly ascertained, both in adults and children. In general, conventional radiological studies indicated that around 40% of both adults and pediatric patients with asthma, have sinus abnormalities; this percentage is even higher in patients with severe asthma and/or longer history of respiratory disease.

Although RS may exacerbate asthma through several mechanisms by contiguity, the interplay between upper and lower airways seems to be much more complex, especially in patients with CRS. Both asthma and CRS are characterized by eosinophilic inflammation, which is more severe in children with this comorbidity than in those affected with CRS, but without asthma. Conversely, patients with difficult asthma resulted to be at greater risk of CRS.

The extension of a primitive and localized eosinophilic inflammatory process to other sections of airways may occur not only by contiguity, but also through systemic mechanisms, which actually may be the most important component. The onset of persistent Th2-driven and eosinophilic inflammation at one site of the airways may release in the bloodstream several cytokines stimulating the bone marrow, which may function as a systemic amplifier of the eosinophilic inflammation.

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