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Inflammation is a defining characteristic of chronic rhinosinusitis and nasal polyposis. Research had traditionally focused on the role of eosinophils in the pathogenic mechanisms, but recently more attention has been given to neutrophils and to different T-lymphocyte subtypes. This article summarizes current understanding, and discusses opportunities and potential pitfalls of inflammation-related research.	
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Chronic rhinosinusitis is a common disease resulting from inflammation of the sinonasal mucosa. It has long been recognized that patients with chronic rhinosinusitis have impaired capacity to clear sinonasal secretions. However, the cause of this pathologic process is not well understood. In this article the components of mucociliary clearance, including cilia, mucus production, and cilia beat frequency, are reviewed and alterations of the system discussed regarding contribution to the disease process.	
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Chronic rhinosinusitis is a complex heterogeneous disease. Infection in the form of biofilm may have an important, if not central, role in the maintenance of the recalcitrant inflammation for this increasingly common chronic disease. Therefore, the importance of understanding the interaction of biofilm disease with the respiratory mucosa is imperative. Novel, minimally invasive methods of testing for the presence of this form of disease will need to become clinically accessible in order for equally innovative therapies to be widely applicable.	
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Chronic rhinosinusitis, including nasal polyps, is an inflammatory disease of the nose and sinuses. The medical treatment, mainly topical intranasal	

and oral corticosteroids, constitutes its first line of therapy. Long-term treatment with corticosteroid nasal spray reduces inflammation and nasal polyp size, and improves nasal symptoms such as nasal blockage, rhinorrhea, and the loss of smell. Corticosteroid intranasal drops may be used when intranasal spray fails to demonstrate efficacy. Short courses of oral steroids are recommended in severe chronic rhinosinusitis with nasal polyps or when a rapid symptomatic improvement is needed. Endoscopic sinus surgery is only recommended when the medical treatment fails. Intranasal corticosteroids should be continued postoperatively. When using intranasal corticosteroids, care should be taken in selected populations such as children, pregnant women, and elderly patients; especially in those patients with comorbid conditions such as asthma, in which the overall steroid intake can be high due to the administration of both intranasal and inhaled corticosteroids.

Aspirin Intolerance: Does Desensitization Alter the Course of the Disease?

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L. Klimek and O. Pfaar

Intolerance to acetylsalicylic acid and to other nonsteroidal anti-inflammatory drugs was first described in 1922. The clinical picture reveals a classic triad of symptoms: aspirin-induced bronchial asthma, aspirin sensitivity, and chronic rhinosinusitis with nasal polyps. In many cases, nasal polyps reveal as the first symptom of ASA sensitivity, indicating that the upper airways are predominantly involved in the pathogenetic process. The emphasis of this article is on the upper airways of ASA-intolerant patients. Imbalance of the eicosanoids leukotrienes and prostaglandins might be the pathophysiologic key to the disease. The patient's history and challenge tests with lysine-aspirin are the diagnostic tools of choice. Apart from surgical or pharmacologic therapy, ASA-desensitization therapy is the treatment of choice. Various desensitization protocols and routes of administration are discussed.

Fungus: A Role in Pathophysiology of Chronic Rhinosinusitis, Disease Modifier, A Treatment Target, or No Role at All?

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Wytske J. Fokkens, Fenna Ebbens, and Cornelis M. van Drunen

Fungal spores, due to their ubiquitous nature, are continuously inhaled and deposited on the airway mucosa. This article focuses on the potential role of fungi in chronic rhinosinusitis (CRS). Five forms of fungal disease affecting the nose and paranasal sinuses have been recognized: (1) acute invasive fungal rhinosinusitis (including rhinocerebral mucormycosis), (2) chronic invasive fungal rhinosinusitis, (3) granulomatous invasive fungal rhinosinusitis, (4) fungal ball (mycetoma), and (5) noninvasive (allergic) fungal rhinosinusitis. There are several potential deficits in the innate and potentially also acquired immunity of CRS patients that might reduce or change their ability to react to fungi. There are not many arguments to suggest a causative role for fungi in CRS with or without nasal polyps. However, due to the intrinsic or induced change in immunity of CRS patients, fungi might have a disease-modifying role.

Anti-Inflammatory Effects of Macrolides: Applications in Chronic Rhinosinusitis 689

Richard J. Harvey, Ben D. Wallwork, and Valerie J. Lund

The anti-inflammatory effects of macrolides are significant. The clinical impact on diffuse panbronchiolitis (DPB) has improved 10-year survival from 12% to more than 90% for these patients. The immunomodulatory activity of macrolides has been a source of mechanistic research as well as clinical research in non-DPB inflammatory airway disease. Suppression of neutrophilic inflammation of the airways has been demonstrated as the most robust immunomodulatory response from 14- and 15-membered ring macrolides. The inhibition of transcription factors, mainly nuclear factor- κ B and activator protein 1, from alterations in intracellular cell signaling drives this mechanism. The suppression of interleukin-8 to a range of endogenous and exogenous challenges characterizes the alterations to cytokine production. The inflammatory mechanisms of chronic rhinosinusitis (CRS) have been a major non-DPB focus. Macrolides have been trialed in more than 14 prospective trials and are the focus of numerous research projects. Evidence for a strong clinical effect in CRS is mounting, but results may be tempered by researchers' inability to characterize the disease process. Eosinophilic dominated CRS is unlikely to respond, based on current research understanding and data from clinical trials. This article discusses the current concepts of macrolides and their application in the management of CRS.

Chronic Rhinosinusitis in Children: What are the Treatment Options? 705

Arthur W. Wu, Nina L. Shapiro, and Neil Bhattacharyya

Pediatric chronic rhinosinusitis, a common problem, has been found to have a severe impact on the quality of life. As in the case with adult chronic rhinosinusitis, pediatric chronic rhinosinusitis is difficult to treat, with resultant frequent recurrences and failures. Controversy has existed in the treatment of chronic rhinosinusitis in children, mirroring the controversy over the exact etiology of this disorder. Chronic rhinosinusitis may indeed be a group of diseases with similar presenting features. This article attempts to delineate treatment options that are both safe and effective for pediatric chronic rhinosinusitis.

When Surgery, Antibiotics, and Steroids Fail to Resolve Chronic Rhinosinusitis 719

Berrylin J. Ferguson, Bradley A. Otto, and Harshita Pant

This article examines the modalities in the treatment of chronic rhinosinusitis (CRS). A correct diagnosis is the first requirement in the successful management of CRS. CRS-directed therapy might fail if the actual cause of symptoms is nonsinogenic. Nasal endoscopy and sinus computed tomography are the primary modalities used in the diagnosis of sinusitis. Allergy and gastroesophageal reflux, may not directly cause sinusitis, but they frequently mimic the symptoms of sinusitis. Therapy can include avoidance of allergens and desensitization in the former and antireflux therapy in the latter. Underlying systemic causes of refractory sinusitis include immunodeficiency and systemic granulomatous and eosinophilic syndromes. Correct diagnosis is essential to directed therapy. Patients

with aspirin exacerbated respiratory disease may benefit from aspirin desensitization. Optimization of mucociliary clearance can be augmented with nasal lavage and mucolytics. Additional nonsteroidal antiinflammatory modalities include use of the leukotriene modulators, montelukast and zileuton. Patients with elevated IgE may benefit from omalizumab (anti-IgE); however, cost constraints restrict use to those patients who have severe asthma. This article also includes management strategies beyond the usual antibiotics, steroids, and sinus surgery. Once immunodeficiency and confounding local mimics of sinusitis are addressed, additional interventions should be tried separately initially to assess the individual patient's response to therapy.

Rhinosinusitis and the Lower Airways

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Peter W. Hellings and Greet Hens

The interaction between upper and lower airway disease has been recognized for centuries, with recent studies showing a direct link between upper and airway inflammation in allergic patients. The mechanisms underlying the interaction between nasal and bronchial inflammation have primarily been studied in allergic disease, showing systemic immune activation after allergen inhalation, induction of inflammation at a distance, and a negative impact of nasal inflammation on bronchial homeostasis. Therefore, allergic rhinitis and asthma are considered part of the global airway allergy syndrome. Besides allergy, other inflammatory conditions such as the common cold, acute rhinosinusitis, and chronic rhinosinusitis are associated with lower airway disease. Chronic sinus disease with or without nasal polyps are frequently found in patients with asthma and chronic obstructive pulmonary disease with improvement of bronchial symptoms and respiratory function by adequate medical and surgical therapy for rhinosinusitis. The resolution of sinonasal inflammation and hence sinonasal functions by medical or surgical treatment is considered responsible for the beneficial effect of treatment on bronchial disease. This article aims at providing a comprehensive overview of the current knowledge on the interaction between common cold, acute and chronic rhinosinusitis, and lower airway biology.

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