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Chapter

The Immunology of Asthma and Allergic Rhinitis

Andrew Kiboneka and Dan Kibuule

Abstract

The immune system is a complex collection of cells, tissues, and chemical mediators positioned throughout the body, whose primary purpose is to protect us against infection. However, its function is not only fundamental in protection from infectious disease but also provides aberrant response in allergens such as with asthma and allergic rhinitis. Allergic diseases like asthma and allergic rhinitis are characterized by a distinct type of inflammatory response, driven by immunoglobulin E (IgE)-dependent mechanisms. In asthma and allergic rhinitis, the inflammatory response is mediated by interaction of several immune cells (monocytes, lymphocytes, and polymorphonuclear cells) and cellular chemical mediators. In particular, atopic allergic response leads to destruction of multiple target cells such as epithelial, parenchymal and vascular and connective tissue of the airways. In addition, in inflammatory response in asthma and allergic rhinitis, sensory nerves are sensitized, leading to clinical manifestations. Sneezing and coughing are hypersensitivity responses of sensory nerves in allergic rhinitis and asthma, respectively. Similarly, nasal congestion and discharge in allergic rhinitis are due to vasodilatation that leads to plasma exudates as well as mucous secretion. The allergic inflammatory response is regulated by several transcription factors, particularly nuclear factor-κB (NF-κB), GATA-3 protein 3, and GATA binding protein.

Keywords: immunology, asthma and allergic rhinitis, TH2 high, TH2 low, IL2 cells, Clara cell secretory protein (CC16), thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, phenotypes, endotypes, united airway hypothesis, biological agents

1. Introduction

Allergic responses are mediated by IgE, a type of antibody associated with mast cells and basophils [1, 2]. Allergic rhinitis (i.e., inflammation of epithelia of nostril) is a reaction to allergens in the environment such as dust, pollen grain, and animal dander, among others. Patients with allergic rhinitis often present with congestion and inflammation (i.e., pain, reddening, and swelling) of the mucous membranes of the upper respiratory tract (nose, throat, eyes, and ears). In contrast, asthma is a complex heterogeneous syndrome characterized by increased inflammatory cells, airway hyper-reactivity (AHR), and structural changes in the lung [3]. The histological features of asthma include edema, cellular infiltration (typically with a prominent T lymphocyte and an eosinophil component), and sub-basement membrane collagen deposition.

Asthma is defined according to the Global Initiative for Asthma (GINA) 2018 as a heterogeneous disease, usually characterized by chronic airway inflammation.
Asthma is induced by an inflammatory response against usually manageable environmental inorganic and organic compounds in the respiratory tract. Indeed, asthma attacks can be triggered by exercise, viral illness, and allergens such as pollen. Other triggers include medications, extremes of weather, stress, smoke, and certain foods. Key indicators include a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation. It has variations in severity, natural history, and response to therapy [4].

Patients diagnosed with atopy have an increased likelihood to allergic responses mediated via IgE, mast cells, and CD4+ lymphocytes. In atopy, the allergic inflammatory responses are mainly due to cytokines (interleukins (IL-3, IL-4, and IL-5)) released from CD4+ lymphocytes. The interleukins increase the IgE production to neutralize the allergens. However, the binding of IgE-allergen complex formed further induces de novo synthesis and release of vasoactive substances that exacerbate the inflammatory reaction. This allergic inflammatory response occurs in two stages (early and late response) in both asthma and allergic rhinitis.

The allergic immune response recognizes allergens via germ line or random encoding, which can be innate and adaptive. The innate allergic immune responses are the first line of defense against allergens that use germ-line encoding and phagocytic cells. In contrast, the adaptive allergic response is mainly designed against infection and allergenic proteins from weed and pollen.

1.1 Pathogenesis of allergic rhinitis and asthma

According to the World Health Organization (WHO), the burden of asthma is estimated to have 300 million cases worldwide, making it one of the commonest noncommunicable diseases. Asthma is a serious global health problem affecting all age groups, with increasing prevalence in developing countries, treatment costs, and a burden for patients and the community. The WHO ranks asthma the highest among chronic illnesses affecting the pediatric population worldwide. Of concern is that the majority of case fatalities attributed to asthma occur among populations in underdeveloped countries characterized with weak health systems for control and management of the disease [4–7].

Whereas allergic rhinitis results from activation of mucosal mast cells, asthma is triggered by allergen activation of submucosal mast cells in the lower airways. The nature and development airway inflammation may be driven by numerous factors, including pathogenic infections, pollution, or even relatively innocuous inhaled particles, such as allergens. International guidelines are available for the management of severe asthma by the European Respiratory Society and the American Thoracic Society [6].

Chronic allergen exposure leads to the continuous presence of increased number of lymphocytes, eosinophils, neutrophils, basophils, and other leukocytes causing airway hyper-reactivity and remodeling—a thickening of the airway walls due to hyperplasia and hypertrophy of the smooth muscle layer, with the eventual development of fibrosis.

It has become apparent that there are many phenotypic and endotype types of asthma. In patients with allergic asthma endotypes, allergen can cause activation of mast cells in an antigen-specific manner. Also allergens can stimulate the airway epithelium, through toll-like receptors (TLRs) and other damage receptors, to release IL-25, IL33, and thymic stromal lymphopoietin (TSLP). These cytokines can lead to the activation of submucosal type two innate lymphoid cells (ILC2), inducing these to release IL-4, IL-5, IL-9, and IL-13.
2. Methodology

A comprehensive review of all aspects of immunology, components of the immune system, immune responses to asthma and allergic rhinitis in children and adults, and airway epithelial cell mucosal immunology was done in a systematic and explicit search of PubMed and HINARI—identifying, selecting, and critically appraising relevant research and textbooks of Immunology from Europe and the United States of America used in undergraduate and postgraduate Medical Education (Cochrane Collaboration) [7–9].

3. Results/findings

Critical analysis of scientific concepts in pulmonary immune inflammation of asthma and allergic rhinitis and an analysis of similarities, differences, and interactions between these two diseases are done.

Knowledge of our immune system functions is critical in understanding allergic airway disease development as well as for selection of appropriate diagnostic and therapeutic options for patients with asthma and allergic rhinitis. A robust inflammatory response is essential to control asthma and allergic rhinitis, and both active and innate mechanisms of immunity are important in this regard. The failure of resolution or persistent pro-inflammatory immune responses results in chronic inflammatory airway diseases like asthma and allergic rhinitis. It is also becoming increasingly important to phenotype airway inflammation in individual patients to allow targeted treatment as we move toward personalized therapies for asthma.

The majority of patients of asthma suffer from an allergic variant of the disease that is triggered by an IgE-driven immune response directed against inhaled antigens and leads to various symptoms, such as wheezing, coughing, and breathing difficulties. The immunopathogenesis of allergic asthma involves a complex interplay between the immune system and parenchymal cells of the lung, including the airway epithelium [10, 11].

Inhaled allergens are phagocytosed by macrophages and dendritic cells (DCs) presented on major histocompatibility complex (MHC) class II molecules and initiate the differentiation of Th2 cells and a humoral immune response. Following class switching, Ag-specific B cells secrete immunoglobulin E which causes degranulation of mast cells.

Cytokines, such as IL-4, IL-5, and IL-13, are produced by TH2 cells, mast cells, basophils, and type 2 innate lymphoid cells, as well as airway epithelial cells, and they trigger pathological events, including airway wall remodeling, bronchial hyper responsiveness, and goblet cell metaplasia. Once the immune response has been initiated, eosinophils become the major effector cells that are responsible for airway dysfunction. In addition to the importance of immune cells in allergic asthma, there is evidence for a prominent role of airway epithelial cells in this disease (Table 1).

3.1 The innate inflammatory immune response and asthma/cells of the immune system

Innate immunity is the body’s immediate response to an infection. It is a non-specific response, meaning that the same response is mounted to a large number of different pathogens. When activated, the innate response is often seen as an inflammatory response. Inflammation is the body’s response to injury or tissue damage.
Rhinosinusitis

Phagocytic cells are a part of the innate immune system and consist of polymorphonuclear cells, monocyte-macrophages, and eosinophils. Neutrophils and monocytes are normally found circulating in the bloodstream and are recruited to sites of infection by the process of extravasation. Receptors on the phagocyte interact with ligands on vascular endothelium, and the cells attach, arrest, and move from the circulation to the diseased tissue/lungs.

Monocytes, similar to neutrophils, can also migrate into the tissues and on doing so differentiate into macrophages. Macrophages have a number of key functions, including phagocytosis of infecting microbes, antigen presentation, and general removal of dying or damaged host cells [12].

3.1.1 Dendritic cells

These are bone marrow-derived cells, found in most tissues, including lymphoid tissues. Discovered by Ralph Steinman in the mid-1970s, dendritic cells are critical for the initiation of the immune response. They are so named, because of being covered with long membranous extensions that resemble the dendrites (extensions) of the nerve cells.

Dendritic cells capture antigens, e.g., pollen/animal dander, and process these antigens and then present them to naïve T cells, initiating the adaptive immune response. The first stage of an immune response to any antigen is the processing and presentation of that antigen by antigen-presenting cells (APCs), e.g., dendritic cells.

3.1.2 Pattern recognition receptors (PRRs)

These are receptors of the innate immune system that recognize common molecular patterns on pathogen surfaces called pathogen-associated molecular patterns (PAMPS), structures that are conserved in broad classes of pathogens for their functional importance. Many of these receptors reside at the plasma

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| C. Bronchial epithelial cells | \begin{itemize} 
- Clara cells
- Ciliated cells
- Goblet cells
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The interleukins IL-25 and IL-33 and thymic stromal lymphopoietin are produced by injured epithelium and play critical roles in driving expression of Th2 cytokines.

Table 1. Classification of the immune system, immune cells, and the inflammatory response in asthma summary of functions.
membrane. They are proteins expressed, mainly, by cells of the innate immune system, such as dendritic cells, macrophages, monocytes, neutrophils, and epithelial cells.

i. One group of receptors, **C-type lectins**, recognizes certain sugar units that are typically located at the terminal position of carbohydrate chains on pathogen surfaces.

ii. Another group and one of the best-characterized signaling PRR families is the evolutionary conserved **toll-like receptor system** in mammals, named after a homologous receptor system used by the *Drosophila* fruit fly for protection from infection. In humans, there are 10 expressed TLR genes in mice [13], their products forming homo- or heterodimers with other family members, thus increasing the repertoire for recognition. TLR4, for example, has been shown to be the receptor recognizing lipopolysaccharide (LPS) found on the surface of Gram-negative bacteria such as *Escherichia coli* but not present on mammalian cells. The effect of pathogen components binding to TLRs on innate immune cells is TLR activation, which initiates signaling into the immune cell and the increased expression of a large number of target genes. The genes involved depend on the pattern of TLRs engaged, but common outcomes include the increased production of inflammatory mediators such as cytokines and chemokines, enhanced phagocytosis (internalization and killing of the pathogen), upregulation of costimulatory molecules on the cell surface, cell migration, and, in the case of macrophages, increased processing and presentation of pathogen antigens to activate an adaptive immune response.

There are also three other families of receptors that sense PAMPS when pathogens arrive in the cytoplasm:

i. **NOD-like receptors (NLRs)**: e.g., NOD1 and NOD2

ii. **RIG-like helicases (RLHs)**: the cytoplasmic RNA-helicase, RIG-I, and related proteins act as virus receptors

iii. **Cyclic GMP-AMP synthase (cGAS, cGAMP synthase):** NB

**Functions of NOD1 and NOD2 and cyclic GMP-AMP synthase:**

- **NLRs** is an acronym that stands for NOD-like receptors. These are a large family of cytosolic proteins activated by intracellular PAMPS. NOD1 and NOD2 recognize important PAMPS, e.g., muramyl dipeptides produced during the synthesis or degradation of either intracellular or extracellular bacteria.

- **cGMP-AMP (cGAMP) synthase (cGAS)** is a cytosolic DNA sensor that activates innate immune responses.

### 3.1.3 Mast cells

A large granule-rich cell found in the connective tissue of the body, most abundantly in the submucosal tissues and the dermis. The granules store bioactive
molecules including the vasoactive amine, which are released on mast cell-activated and are involved in the pathogenesis of bronchoconstriction in asthmatic airways [13, 14].

3.1.4 Eosinophils

A type of white blood cell containing granules that stain with eosin and is an effector cell in asthma as well as produces cytokines, e.g., IL-5 [15, 16]. In the airway of asthmatic patients, eosinophil-derived mediators of inflammation, including eosinophil-derived neurotoxin (EDN), major basic protein (MBP), and lysophospholipase (LPL), are toxic to the respiratory epithelium contributing to the immune pathogenesis of asthma in both children and adults [16].

3.1.5 Basophils

A type of white blood cell containing granules that stain with basic dyes. Basophils are non-phagocytic granulocytes. In response to binding of circulating antibodies, basophils release their contents including histamine which cause smooth muscle contraction in asthmatic airways as well as increasing blood permeability which may account for edema of the airways in asthma and inflammation [17, 18]. Basophils and mast cells release mediators of immediate hypersensitivity, e.g., histamine. Basophils are present in the blood stream, whereas mast cells are present only in the tissue.

3.1.6 Natural killer cells

A type of innate lymphoid cell (ILC) that is important in innate immunity to viruses and other intracellular pathogens and in antibody-dependent cellular cytotoxicity (ADCC) hypersensitivity reactions.

They do not express antigen receptors and are considered part of the innate immune system, despite being lymphoid cells [19, 20].

3.1.7 NKT cells

Is another type of cell in the lymphoid lineage that shares features with both conventional T lymphocytes and NK cells like T cells; NKT cells have T-cell receptors (TCRs) and some express CD4. Unlike most T cells, however, the TCRs of NKT cells are not very diverse and recognize specific lipids and glycolipids presented by a molecule related to the major histocompatibility complex (MHC) proteins called CD1.

Like their innate immune counterparts, NK cells, NKT cells have antibody receptors.

NKT cells are considered as a cell subset belonging to the innate immune system with the capacity to amplify adaptive immune responses in asthma [7–9, 21].

Defining the roles of thymic stromal lymphopoietin, IL-25, and IL-3 in human asthma:

IL-25, IL-33, and TSLP are epithelial-derived cytokines and have been identified as having an important role in asthma pathogenesis. These cytokines have been described as epithelial-derived alarmins that activate and potentiate the innate and humoral arms of the immune system in the presence of actual or perceived damage. TSLP is increased in asthmatic airways, mast cells and in the lungs is produced mainly by airway epithelial cells. In addition, these three cytokines can generate a H2 cytokine profile independent of the adaptive immune system. TSLP is a
TH2-promoting cytokine that significantly contributes to the immune pathogenesis of asthma [22–24].

3.1.8 IL-33

Interleukin-33 (IL-33), which belongs to the larger family of damage-associated molecular pattern molecules, has been considered as an “alarmin” [22–24]. It is released to alert the immune system by first-line cells, such as tissue epithelial cells.

3.1.9 IL-C2

Innate lymphoid cells are a group of lymphoid cells with a recently recognized role as regulators of innate immunity, inflammation, and tissue repair at the barrier surfaces. They are a lymphoid subclass characterized by the lack of either B- or T-cell receptors but retain cytotoxic or immunomodulatory capacity [22–24].

The innate defense system contains cells that look just like B or T lymphocytes under the microscope, yet express neither B- nor T-cell receptors. These cells are known as innate lymphoid cells.

Innate lymphoid cells are classified into three groups based on their transcription factors and cytokine production patterns, which mirror helper T-cell subsets. Unlike T cells and B cells, ILCs do not have antigen receptors. They respond to innate factors released by the bronchial epithelium, such as cytokines and alarmins, including IL-33, IL-25, and thymic stromal lymphopoietin [22–24]. ILCs produce multiple pro-inflammatory and immune regulatory cytokines for the induction and regulation of inflammation.

3.1.10 CC16 club cells/Clara cells

Clara cells are non-ciliated, non-mucous, secretory cells in respiratory epithelium. These epithelial cells secrete several distinctive proteins, including Clara cell 10-kDa secretory protein (CCSP). Clara cells are most predominant in the terminal and respiratory bronchioles of humans.

Club cells, also known as bronchiolar exocrine cells and originally known as Clara cells, are dome-shaped cells with short microvilli, found in the small airways (bronchioles) of the lungs.

Of recent Clara cells (CC16) have re-emerged in the immune pathogenesis of Asthma [25].

3.2 The adaptive inflammatory cells

T-cell responses to antigens consist of a combination of pro-inflammatory (effector) and anti-inflammatory (regulatory) cells.

- Lymphocytes differentiate into separate lineages. The B lymphocytes secrete antibodies.

The T lymphocytes operate in a supervising role to mediate cellular and humoral responses. Antigen presentation describes a vital immune process which is essential for T-cell immune response triggering immunity. B and T lymphocytes produce and express specific receptors for antigens. Collectively, the functions of the T and B cells encompass an entity called the adaptive immune system.

T-helper lymphocytes conventionally are TH1 and TH2 cells. TH1 cells produce cytokines that downregulate the atopic response. In those who are genetically susceptible to developing asthma, antigen presentation to T-helper cells leads to a
TH2 response, pro-inflammatory cytokines, and upregulation of airway inflammation of asthma by enhancing immunoglobulin E synthesis, eosinophils, and mast cell activation/function.

3.2.1 TREG cells

TREG cells, a type of T-helper lymphocytes, bind interleukins 2 via the CD25 and CD45RB receptors to signal suppression of the immune system. This is essential in arresting inflammatory allergic responses such as in asthma and allergic rhinitis. In addition, naive T lymphocytes are induced to synthesize FoxP3 which acts as a transcription factor for the cytokines involved in the TREG-mediated cascade. In particular, transforming growth factor-β (TGF-β) and interleukin-10 are the main cytokines implicated in the TREG-mediated suppression of inflammatory allergic responses [26, 27]. Thus, TREG cells are critical in the autoregulation of allergic inflammatory reactions by slowing the pathological effects of the Th2 type immune responses in bronchial hyper-reactivity and inflammation in asthma [26–28].

3.3 The respiratory airway cells/mucosal immunology

There are several cells in the epithelium of the lower respiratory tract. The upper part includes support cells (basement), mucous-secreting cells, and the cilia, to aid the expulsion of mucous. However, Clara cells and cilia dominate in the lower parts of the respiratory system [29, 30]. Some of these cells are involved in inflammatory allergic responses in asthma. For instance, in asthma the goblet cells, i.e., mucous-secreting cells, increased the number of goblet cells as part of airway remodeling. The mucus (i.e., a complex solution of lipids and proteins in the airways) aggravates the immunopathology of asthma. The function of mucus is to trap inhaled particles/allergen and the interaction with the tips of beating cilia and remove particles/allergen from the airways, a process termed mucociliary clearance [31]. Other cells such as the neuroendocrine cells are not directly involved in the immunopathogenesis of asthma. Neuroendocrine cells (i.e., small round cells with dark staining nucleus and clear cytoplasm) contain characteristic granules and secrete hormones and peptides such as serotonin.

In particular, lymphoid tissues are mainly found in the bronchial. Thus during an asthmatic attack, the airways are remodeled (i.e., bronchial thermoplasty), which is characterized by swelling, cellular infiltration, and hyperplasia of smooth muscles and goblet cells [7–9]. The adaptation (i.e., hypertrophy, metaplasia, fibrosis, and hyperplasia) of the epithelial airways and smooth muscle cells to allergic and/or noxious stimuli compromises the structure and function of the airways [31, 32].

Indeed, the epithelial cells are important in providing rapid response to counter allergens by secreting mucous and initiating the inflammation. This epithelium provides a barrier against the external environment and protects against infection from airborne pathogens. Defective barrier function or viral infection can lead to respiratory tract disease like asthma.

The first line of defense against invasion by potential pathogens is the thin layer of epithelium that covers mucosal surfaces including that of the upper and lower respiratory tract. The mucosal immune system has unique features including large size, uptake, and presentation of antigen and contains a large number of effector T lymphocytes. The circulation of lymphocytes within the mucosal immune system is controlled by tissue-specific adhesion molecules and chemokine receptors.
The analysis of molecular markers of airway inflammation has provided promising and noninvasive techniques that facilitate the detection of disease phenotypes as well as measurement of therapeutic efficacy for asthma.

Current treatments for severe forms of asthma have been extended to the use of biological modifiers for the classical asthma endotypes (i.e., Th2 high and Th2 low). Conventional immune modulators (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) used in the management of severe forms of asthma are for patients with asthma of the type Th2 high. The inflammatory in patients with Th2 high asthma is principally mediated by eosinophil reactions as well as type 2 cytokines (i.e., IL-4, IL-13, IL-5) produced by Th2 cells. The type 2 cytokines are in turn regulated by other interleukins, namely, IL-25 and IL-33, as well as TSLP [9, 10]. These mediators are upstream innate factors that drive IL-13 and IL-5 production.

In contrast, TH2 low asthma is poorly described. Patients do not have eosinophilia and other markers but have neutrophilia inflammation. This is mainly due to the activation of TH1 or 17 cells that release IFN and IL-17. These cells are specifically produced at mucosal surfaces and thus are important in airway inflammation. The role of ILCs, more specifically type 2 ILCs, in the pathogenesis of allergic airway diseases has been extensively investigated over the last decade. Chronic nasal inflammation may aggravate or lead to the development of other significant disorders, including asthma, rhinosinusitis, and middle ear disease.

3.3.1 Allergic rhinitis and mediators of the inflammatory response

Sensitization is initiated in nasal tissues when antigen that is deposited on the nasal mucosa is engulfed by antigen-presenting cells—macrophages, dendritic cells, Langerhans cells—and partially degraded within their phagolysosomes into antigenic peptides. These peptides are then externalized on the surfaces of APCs and are presented to naïve CD4+ T lymphocytes. The interaction of T-helper lymphocytes is activated by presentation of an allergen via the MHC class II receptor on macrophages and other cells [32–34].

In patients with allergic rhinitis, allergen-triggered early and late responses are mediated by a series of inflammatory cells. Within minutes of contact with allergen, IgE-sensitized mast cells degranulate, releasing both preformed and newly synthesized mediators. Immunologic processes in both nasal and bronchial tissues involve TH2 lymphocytes and eosinophils. Eosinophils are the predominant cell in the chronic inflammatory process characteristic of the late-phase allergic response. Eosinophils release an array of pro-inflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and might serve as a major source of IL-3, IL-5, GM-CSF, and IL-13. Neuropeptides also appear to contribute to the pathophysiology of allergic rhinitis symptoms.

3.3.2 Allergen exposure

The respiratory tract is an important route of allergen entry. Several people react to airborne allergens with an IgE-mediated reaction, resulting from the deposition of mucosal mast cells beneath the nasal epithelium by allergens such as pollen that when they contact the epithelium, they release their soluble protein content, which is rich in eosinophils and allergic rhinitis characterized by intense itching, sneezing, nasal blockage, and irritation of the nasal mucosa due to histamine release.

In atopic-related allergic rhinitis, the hypersensitivity mediated via IgE, mast cells, and lymphocytes is inherited. The continued exposure of allergens initiates
the inflammatory process via the APC, lymphocytes, and cytokine cascades (i.e., IL-3, IL-4, and IL-5). Until then, the immune system is not yet sensitized to the allergen. Following sensitization, further exposures initiate the inflammatory/allergic response and clinical presentation of allergic rhinitis.

3.3.3 United airway hypothesis/disease

Upper and lower airways are considered a unified morphological and functional unit, and the connection existing between them has been observed for many years, both in health and in disease [35]. The respiratory system is integrated, and thus the allergic diseases of the lower (i.e., asthma) and the upper respiratory tract (allergic rhinitis) have similar pathogenesis and should be considered as one. Indeed, precious studies have shown an overlap in the clinical presentation of these two diseases where patients with allergic rhinitis are at risk for asthma.

4. Conclusions

Asthma and allergic rhinitis are a complex heterogeneous group of airway diseases that affects both children and adults worldwide. Through the use of molecular and cellular immunology, conceptual shifts have been made in the understanding of these diseases involving both innate and adaptive immunity as well examination of airway epithelial changes that occur with asthma, evolving into personalized-targeted therapy for asthma in view of these mechanisms. Allergic rhinitis is the most common of all atopic diseases, and although it can develop at any age, most patients report the onset of symptoms before 30 years of age, making it the most common chronic disorder in children.

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Conflict of interest

No conflict of interest to declare.

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Rhinosinusitis

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