Asthma: Clinical expression and molecular mechanisms

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Asthma is a complex disorder that displays heterogeneity and variability in its clinical expression both acutely and chronically. This heterogeneity is influenced by multiple factors including age, sex, socioeconomic status, race and/or ethnicity, and gene by environment interactions. Presently, no precise physiologic, immunologic, or histologic characteristics can be used to definitively make a diagnosis of asthma, and therefore the diagnosis is often made on a clinical basis related to symptom patterns (airways obstruction and hyperresponsiveness) and responses to therapy (partial or complete reversibility) over time. Although current treatment modalities are capable of producing control of symptoms and improvements in pulmonary function in the majority of patients, acute and often severe exacerbations still occur and contribute significantly to both the morbidity and mortality of asthma in all age groups. This review will highlight some of the important clinical features of asthma and emphasize recent advances in both pathophysiology and treatment.
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Abbreviations used
API: Asthma predictive index
EBC: Exhaled breath condensate
EIB: Exercise-induced bronchospasm
GERD: Gastroesophageal reflux disease
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
NSAID: Nonsteroidal anti-inflammatory drug
RBM: Reticular basement membrane
RSV: Respiratory syncytial virus

Asthma is a heterogeneous disorder that is characterized by variable airflow obstruction, airway inflammation and hyperresponsiveness, and reversibility either spontaneously or as a result of treatment. Multiple etiologies no doubt exist for both its inception and symptom exacerbation once the disease is established. Factors underlying inception can range from viral respiratory tract infections in infancy[1,2] to occupational exposures in adults.[3] Factors underlying asthma exacerbations include allergen exposure in sensitized individuals, viral infections, exercise, irritants, and ingestion of nonsteroidal anti-inflammatory agents, among others. Exacerbating factors can include one or all of these exposures and vary both among and within patients. Asthma treatment is determined to a large extent after an initial assessment of severity and subsequent establishment of control, both of which can be variable over time and assessed in 2 domains: impairment (current) and risk (long-term consequences).[4] Unfortunately, despite the availability of effective therapies, suboptimal asthma control exists in many patients on a worldwide basis.[5] The future development of novel therapies and treatment paradigms should address these disparities.

NATURAL HISTORY (INCEPTION AND PROGRESSION)

For many asthmatic subjects, the disease has its roots during infancy and early childhood. Viral respiratory tract infections produce wheezing episodes during the first 3 years of life in about 50% of children.[6] Some of these children will stop wheezing (transient wheezers), whereas others will go on to have persistent symptoms that will either dissipate before adolescence (primarily nonatopic subjects) or continue into adolescence (atopic wheezers).[7] Once in remission, the disease process might remain quiescent, or the subject could relapse in later life.[8,9] The phenotype of severe asthma has also been recently well described.[10]

The pattern and rate of loss of lung function in asthmatic subjects has been of interest and concern for many investigators. A number of groups have reported that the greatest absolute loss of lung function appears to occur very early in childhood.[8,11,12] Some have reported that the peak in lung function that is achieved at about 20 years of age in asthmatic subjects can be decreased[13] and that the rate of further loss during adulthood can be increased in asthmatic subjects.[14] About one fourth of children with asthma might experience greater rates of loss of lung function, and these children have certain phenotypic characteristics: younger age, male sex, higher postbronchodilator FEV_1 percent predicted, and greater airway eosinophilic inflammation.[15]

Molecular and cellular mechanisms in asthma

Children. The performance of invasive procedures in children to evaluate molecular and cellular mechanisms in asthma is

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obviously not as feasible from a variety of standpoints compared with adults. However, a few carefully and safely conducted studies in young children have provided insights into possible pathophysiologic features as they relate to developmental milestones and disease expression. When bronchoalveolar lavage has been performed in young wheezing children, a 3-fold increase in total cells, most significantly lymphocytes, polymorphonuclear cells, and macrophages/monocytes, compared with counts seen in healthy children has been noted. In addition, levels of leukotriene B_4 and C_4, prostaglandin E_2, and the potentially epithelium-derived 15-hydroxyeicosattetranoic acid were all increased.[16]

Several bronchial biopsy studies have been performed in children. In 53 infants with reversible airflow obstruction evaluated for severe wheezing or cough, bronchial biopsy specimens demonstrated no reticular basement membrane (RBM) thickening or the eosinophilic inflammation characteristic of asthma in older children and adults, even in the presence of atopic characteristics.[17] Conversely, children younger than 6 years with asthma had increased epithelial loss, basement membrane thickening, and eosinophilia compared with control subjects of the same age. However, similar pathologic changes were seen in atopic children without asthma.[18] Taken together, it appears that the inflammatory and structural changes associated with asthma occur sometime after infancy during the early preschool years, when children experience more persistent symptoms of airway dysfunction.

In older children 6 to 16 years of age with difficult asthma receiving high-dose inhaled corticosteroids (ICSs), RBM thickening to a similar extent to that seen in adult asthmatic subjects has been demonstrated.[19] Additionally, there was no association with RBM thickening and age, symptom duration, lung function, or concurrent eosinophilic airway inflammation. However, unlike adults with asthma, no relationship was observed between RBM thickness and bronchial wall thickening on high-resolution computed tomographic scanning in children with difficult asthma.[20] Finally, persistent airflow obstruction has been associated with a greater density of $CD4^+$ T lymphocytes in endobronchial biopsy specimens in 27 school-aged children with difficult asthma after treatment with systemic corticosteroids compared with that seen in control subjects.[21]

A number of biomarkers have been evaluated to avoid the invasive procedures of bronchial lavage, biopsy, or both in children. Exhaled nitric oxide might be useful as a diagnostic tool and in ongoing management of children with asthma. Exhaled nitric oxide levels have been demonstrated to differentiate young children with asthma from those without,[22] to identify children who are likely to respond to ICSs,[23] and to predict those children who will experience an asthma relapse after reduction of ICSs.[24] However, recent data indicate that when fraction of exhaled nitric oxide monitoring is used in conjunction with a National Asthma Education and Prevention Program guidelines–based asthma management program, it might result in excessive ICS dosing without any significant gains in achieving or maintaining asthma control.[25]

Exhaled breath condensate (EBC) is obtained by cooling exhaled air and is believed to reflect the contents of the airway lining fluid.[26] Hydrogen peroxide, isoprostanes, aldehydes, and nitrotyrosine are considered markers of oxidative stress, and their levels are increased in the EBC of children with asthma, suggesting an imbalance between oxidants and antioxidants. Conversely, levels of glutathione, a protective lung antioxidant, are decreased in children with acute asthma, suggesting a reduced antioxidant capacity.[27] Levels of the inflammatory mediators cysteinyl leukotrienes are increased in the EBC of children with atopic asthma, even while receiving corticosteroid treatment.[28] Finally, airway pH balance might have a role in asthma because a reduced EBC pH has been reported in children with acute or stable asthma.[26]

Levels of several other mediators of inflammatory cells have been found to be significantly higher in very young children with asthma, including the number of blood eosinophils, serum eosinophil cationic protein, eosinophil-derived neurotoxin, and urinary eosinophil-derived neurotoxin.[29] In addition, both increased eosinophil cationic protein and cysteinyl leukotriene levels[30] have been obtained from nasal washings in wheezing children less than 2 years of age.

Adults. Asthma for most, but not all, patients begins in early life. As noted above, the cellular and molecular patterns associated with airway inflammation in asthma are complex, interactive, redundant, and variable.[31] In adults, particularly those with established longstanding disease, the factors that contribute to the pathophysiology of airway abnormalities are dependent on the phases of asthma, such as acute, persistent, severe versus nonsevere, or during treatment.

An understanding of the immunopathology of airways in asthma has been markedly advanced with the use of bronchoscopy and biopsy. These airway samples can then be analyzed by using histologic and immunologic methods, and the identified features can be evaluated in relationship to clinical features of asthma to more fully understand the contribution of cellular and molecular events to the resulting physiology and response to treatment.[32] In addition, it is now appreciated that the regulation of airway inflammation is distinct in different phases of asthma (ie, early-onset disease largely related to allergic inflammation and in the persistent or chronic phase of the disease).[33] It is helpful to arbitrarily consider asthma in terms of the traditional T_H2 inflammatory processes and the more chronic inflammatory phase, in which resident airway cells assume the more dominant component contributing to airway dysfunction (Fig 1),[33] to appreciate the immunopathogenetic mechanisms associated with different phases of asthma.

In the acute inflammatory aspects of asthma, allergen-IgE–directed processes are predominant features of airway pathology, with mast cells, T_H2 lymphocytes, and eosinophils the predominant histologic features.[32] The cytokine network associated with these processes often includes IL-3, IL-4, IL-5, IL-9, and IL-13.[34] Mast cells are important contributors both to the initiation of asthma with release of acute-phase mediators, including cysteinyl leukotrienes, and also inflammatory cytokines, which serve to perpetuate inflammatory events in the airway.[35] Subpopulations of lymphocytes polarized toward a T_H2 profile further the inflammatory process by release of cytokines, including IL-4, IL-5, and IL-13. It is these factors that serve to drive inflammation (eg, recruitment of eosinophils) and also regulate IgE production.[32]

Eosinophils are a characteristic feature of allergic inflammation.[32] The biology of eosinophils is well designed to cause airway inflammation, enhancement of airway hyperresponsiveness, and airflow obstruction. Eosinophils are recruited to the airway in asthmatic subjects by families of cytokines, and chemokines (eg, IL-5, RANTES, and eotaxin) undergo cell activation through processes not fully identified and release highly inflammatory granule-associated substances, the actions of which injure the airway and cause persistent inflammation. Eosinophils