

INTRODUCTION

The atopic diseases of childhood consist of the triad of asthma, allergic rhinitis and atopic dermatitis. All share a common pathogenesis being mediated by IgE and are frequently present together in the same individual and family (*Stone, 2002*).

Over the past several decades, the incidence of atopic diseases such as asthma, atopic dermatitis and food allergy has increased dramatically. Among children up to 4 years of age, the incidence of asthma has increased 160%, and the incidence of atopic dermatitis has increased twofold to threefold (*Eichenfield et al., 2003*).

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE) mediated inflammation of the membranes lining the nose (*Bousquet et al., 2001*). Allergic rhinitis is the most common type of chronic rhinitis, affecting 10 to 20% of the population, and evidence suggests that the prevalence of the disorder is increasing. Severe allergic rhinitis has been associated with significant impairments in quality of life, sleep and work performance (*Dykewicz et al., 2010*).

Asthma is a chronic episodic disease, characterized by acute symptomatic episodes of varying severity, occasionally near fatal or fatal. Since the 1970s, the frequency and severity

of asthma has increased in a considerable number of countries in both children and adults (*Weiss et al., 2001*).

Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with cutaneous hyper-reactivity to environmental triggers that are not harmful to non-atopic individuals (*Leung et al., 2003*).

Atopic dermatitis (AD) usually presents during early infancy and childhood but it can persist into or start in adulthood (*Spergel et al., 2003*). Various studies indicate that AD has a complex etiology with activation of multiple immunologic and inflammatory pathways (*Novak et al., 2003*).

Interleukin-33 (IL-33) is a recently discovered cytokine that belongs to the IL-1 super-family and is mainly expressed by different types of structural cells (*Yasuoka et al., 2011*).

Interleukin-33 expression was found to be increased in several pathological conditions such as airway smooth muscle cell and lung epithelial cells of asthmatic patients (*Prefontaine et al., 2010*). IL-33 also seems to be essential for development of allergic rhinitis induced by ragweed pollen challenge (*Haenuki et al., 2012*).

Interleukin-33 is considered to be linked to the development of several allergic diseases such as asthma and atopic dermatitis (*Cho et al., 2012*).

AIM OF THE WORK

This study aim to evaluate measurement of the serum level of Interleukin-33 (IL-33) in patient of allergic diseases e.g bronchial asthma, allergic rhinitis, atopic dermatitis and angioedema. The ultimate objective is to study the prognostic gain from adding this marker to the work up of this diseases.

Chapter One

PEDIATRIC ATOPIC DISEASES

The word atopy refers to an inherited tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of common environmental proteins such as pollen, house dust mite, and food allergens. The presence of atopy in an individual is associated with an increased risk of developing one or more of the atopic diseases atopic dermatitis, asthma, allergic rhino-conjunctivitis/ hay fever and food allergy. However, atopy can be present in the form of asymptomatic sensitization to one or more allergens, which means that an individual with confirmed allergic sensitization does not exhibit clinical allergy. Sensitization is common in the atopic diseases of childhood and is less frequent in adults with atopic disease, particularly in those with adult-onset atopic disease (*Reed, 2006*).

Asymptomatic sensitization to aeroallergens, however, is a strong predictor for future development of allergic symptoms, while allergic symptoms in non-sensitized subjects are a much lower risk factor for subsequent sensitization (*Bodtger et al., 2006*).

Atopy and atopic diseases run in families and a positive family history is a strong risk factor for developing atopic disease (*Apfelbacher et al., 2011*).

Tamari et al. (2013) determined the genetic components of these diseases and many genes have been identified. However, the increasing prevalence of atopic diseases cannot be explained by genetic factors alone and the increase together with the large differences in prevalence between urban and rural regions points towards environmental factors.

I- Bronchial asthma:

Asthma is a chronic inflammatory disease with histologic lesions in bronchial wall. It affects all ages, characterized by infiltration of mast cells, re-versible airflow obstruction, airway hyperreactivity, and airway remodeling (*Lai et al., 2015*).

Another definition by *GINA (2017)*, Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the 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.

Asthma phenotypes:

Asthma is a heterogeneous disease, with different underlying disease processes. Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'. In patients with more severe asthma, some phenotype-guided treatments are available (*Wenzel, 2012*).

Many phenotypes have been identified. Some of the most common include:

- **Allergic asthma:** This is the most easily recognized asthma phenotype, which often commences in childhood and associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to Inhaled Corticosteroid (ICS) treatment.
- **Non-allergic asthma:** Some adults have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic). Patients with non-allergic asthma often respond less well to ICS.

(Wenzel, 2012)

Pathogenesis of asthma:

In allergic asthma, genetically susceptible individuals respond to environmental allergens with inappropriate T-cell-mediated immune responses, leading to chronic obstruction of the airways (**figure 1**) (*Holgate and Polosa, 2006*). Allergic asthma is characterized by the accumulation of inflammatory infiltrates in the lung, airway hyper-responsiveness to a variety of specific and non-specific stimuli, increased serum Ig-E

levels, and mucus hypersecretion. Chronic inflammation further leads to structural changes (airway remodeling) with collagen deposits, hyperplasia, and thickening of the airway wall. In asthmatic patients, allergic episodes trigger the bronchoalveolar infiltration of various immune cell populations, mostly eosinophils and mast cells. Effector T-helper 2 (Th2) cells play a central role in orchestrating the immune response to allergens by releasing cytokines that trigger the predominant features of asthma **(figure 2)**: The secretion of IL-4 and IL-13 contributes to B-cell production of IgE, the release of IL-5 drives eosinophilic inflammation, and IL-9 stimulates mast cell proliferation **(Rosenberg et al., 2007)**.

The action of IL-4 and IL-13 on lung epithelial further induces goblet cell metaplasia, whereas IL-13 acting on smooth muscle cells promotes the development of airway hyper-responsiveness. Other subsets of T-helper cells have been linked to asthma pathogenesis, including Th9, Th25, and Th22 cells **(Nakagome et al., 2011)**.

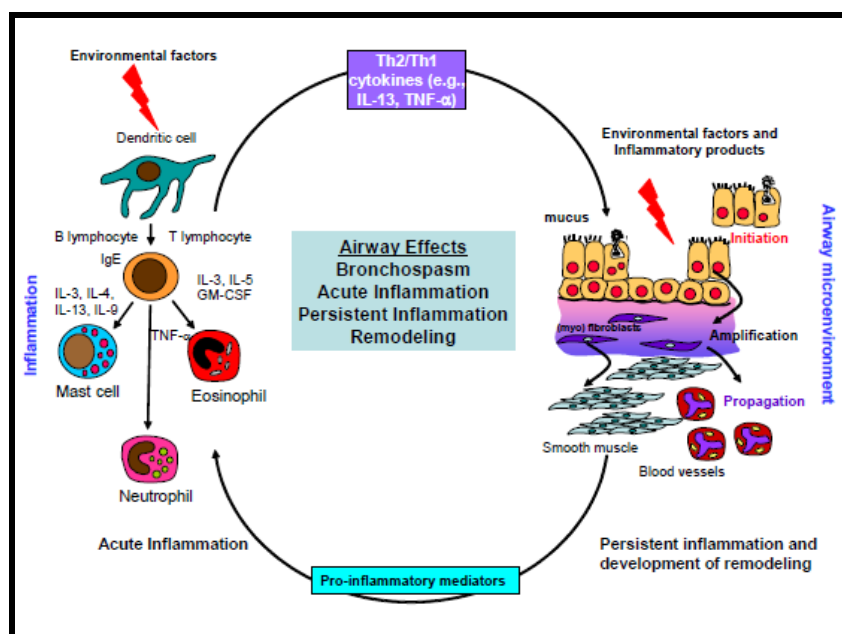


Figure (1): Factors limiting airflow in acute and persistent asthma (Holgate and Polosa, 2006).

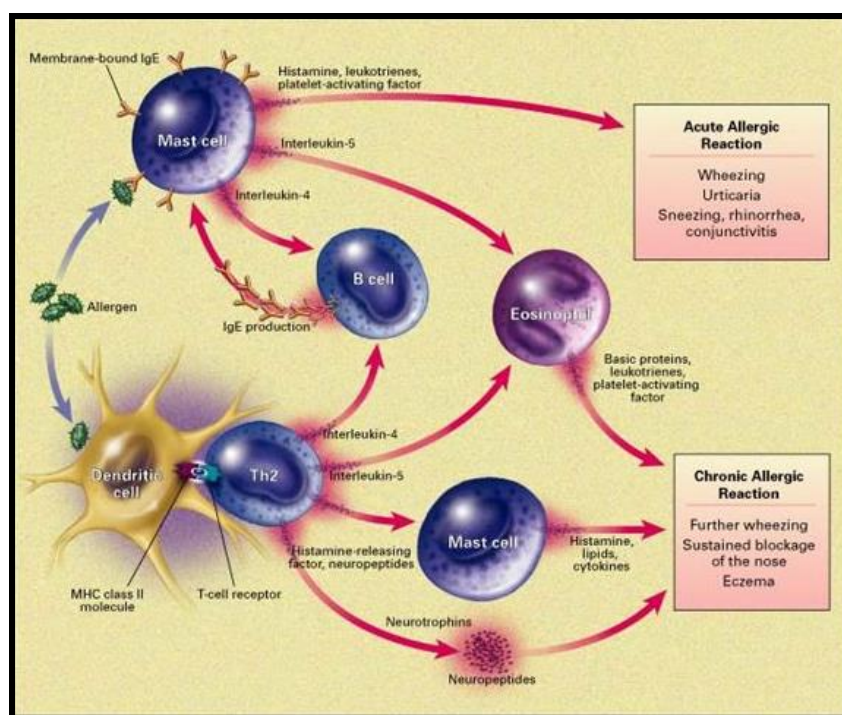


Figure (2): Pathways leading to acute allergic reactions (Kay, 2001).

A subset of lung-infiltration T-cells known as Th17 cells has been described to account for neutrophilic airway inflammation, but also for enhanced Th2-cell mediated eosinophilic airway inflammation (**figure 3**). IL-17 secretion by both Th-17 cells and eosinophils was further found to be increased in asthmatic patients (*Levine and Wenzel, 2010*).

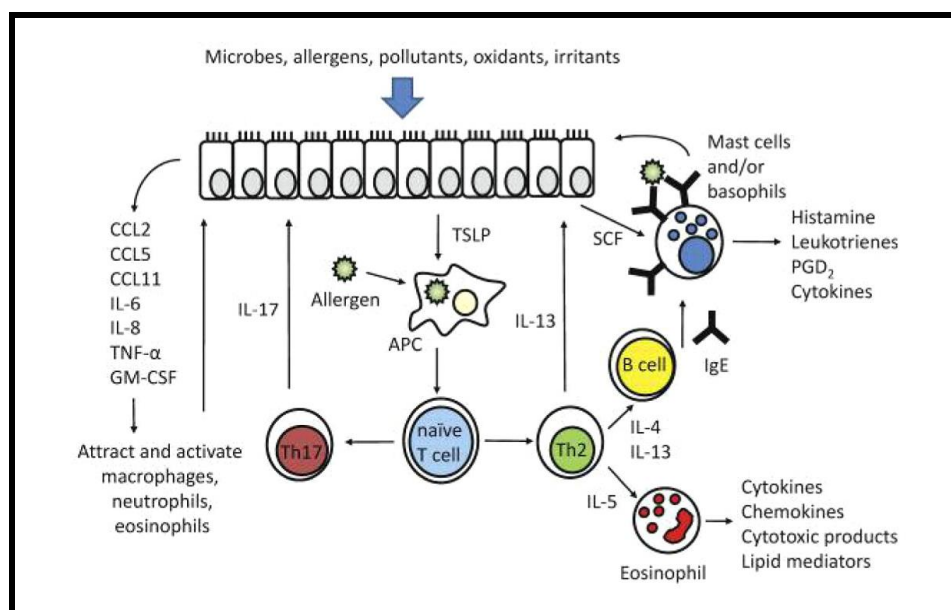


Figure (3): Pathogenesis of allergic asthmatic inflammation. Abbreviations: CCL, chemokine ligand; GM-CSF, granulocytemacrophagecolony-stimulating factor; PGD₂, prostaglandin D₂; SCF, stem cell factor; TNF- α , tumor necrosis factor-alpha (*Levine and Wenzel, 2010*).

Although asthma is generally considered to be an adaptive immune disorder, the innate arm of the immune system also contributes to the pathology through the production of pro-inflammatory mediators by bronchial epithelial cells, mast cells, basophils, Natural Killer T (NKT) cells, and Dendritic Cells (DC) (*Ono et al., 2010*).

There is ample evidence that a variety of suppressive and regulatory mechanisms are crucially involved in preventing the activation of potentially harmful effector responses in the lungs of healthy individuals (*Ray et al., 2010*).

Commencement of respiratory symptoms in childhood, a history of allergic rhinitis or eczema, or a family history of asthma or allergy, increases the probability that the respiratory symptoms are due to asthma. However, these features are not specific for asthma. Patients with allergic rhinitis or atopic dermatitis should be asked specifically about respiratory symptoms (*GINA, 2017*).

Diagnosis of asthma

The diagnosis of asthma should be based on history of characteristic symptom patterns and evidence of variable airflow limitation, from bronchodilator reversibility testing or other tests. Increased probability that symptoms are due to asthma if more than one type of symptom (wheeze, shortness of breath, cough, chest tightness), symptoms often worse at night or in the early morning, symptoms vary over time and in intensity, symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, irritants such as car exhaust fumes, smoke, or strong smells (*GINA, 2017*).

Physical examination in asthma

Often normal, the most frequent finding is wheezing on auscultation, especially on forced expiration. Wheezing is also found in other conditions, for example respiratory infections,

COPD, upper airway dysfunction, endobronchial obstruction, inhaled foreign body, wheezing may be absent during severe asthma exacerbations ('silent chest') (*GINA, 2017*).

Assessing asthma severity

Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations, assess asthma severity after patient has been on controller treatment for several months, severity is not static – it may change over months or years, or as different treatments become available. Categories of asthma severity include:

Mild asthma: well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS). Moderate asthma: well-controlled with Step 3 (low-dose ICS/LABA). Severe asthma: requires Step 4/5 (moderate or high dose ICS/LABA $\pm$ add-on), or remains uncontrolled despite this treatment (*GINA, 2017*).

Level of asthma symptoms control

In the past 4 weeks has the patient had:

1. Day time asthma symptoms more than twice a week.
2. Reliever needed for symptoms more than twice a week
3. Any night waking due to asthma.
4. Any activity limitation due to Asthma.

The patient considered Well controlled if has none of these, partially controlled if has one or two of these and is not controlled if has three or four of these symptoms (*GINA, 2017*).

Treatment of bronchial asthma:

Table (1): Recommended options for initial controller treatment

Preferred initial controller	Presenting symptoms
No controller*	Asthma symptoms or need for SABA less than twice a month; no waking due to asthma in last month; and no risk factors for exacerbations, including no exacerbations in the last year
Low dose ICS	Infrequent asthma symptoms, but the patient has one or more risk factors for exacerbations e.g. low lung function, or exacerbation requiring OCS in the last year, or has ever been in intensive care for asthma
Low dose ICS	Asthma symptoms or need for SABA between twice a month and twice a week, or patient wakes due to asthma once or more a month
Low dose ICS Other less effective options are LTRA or theophylline	Asthma symptoms or need for SABA more than twice a week
Medium/high dose ICS or low dose ICS/LABA**	Troublesome asthma symptoms most days; or waking due to asthma once a week or more, especially if any risk factors exist
Short course of oral corticosteroids and start regular controller treatment; options are: ▪ High-dose ICS or ▪ Moderate-dose ICS/LABA**	Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation
Before starting initial controller treatment	
▪ Record evidence for the diagnosis of asthma, if possible. ▪ Record the patient's level of symptom control and risk factors, including lung function. ▪ Consider factors influencing choice of treatment. ▪ Ensure that the patient can use the inhaler correctly. ▪ Schedule an appointment for a follow-up visit.	
After starting initial controller treatment	
▪ Review patient's response after 2-3 months, or earlier depending on clinical urgency. ▪ Step down treatment once good control has been maintained for 3 months.	

ICS: Inhaled Corticosteroids; LABA; Long-Acting Beta₂-agonist; LTRA: Leukotriene Receptor Antagonist; OCS: Oral Corticosteroids; SABA: Short-Acting Beta₂-Agonist.

*These recommendations reflect the evidence for chronic airway inflammation in asthma even when symptoms are infrequent, the known benefit of low dose ICS in reducing serious exacerbations in broad asthma populations, and the lack of large studies comparing the effect of ICS and as-needed SABA alone on exacerbations in these populations.

**Not recommended for initial treatment in children 6-11 years.

(GINA, 2017)

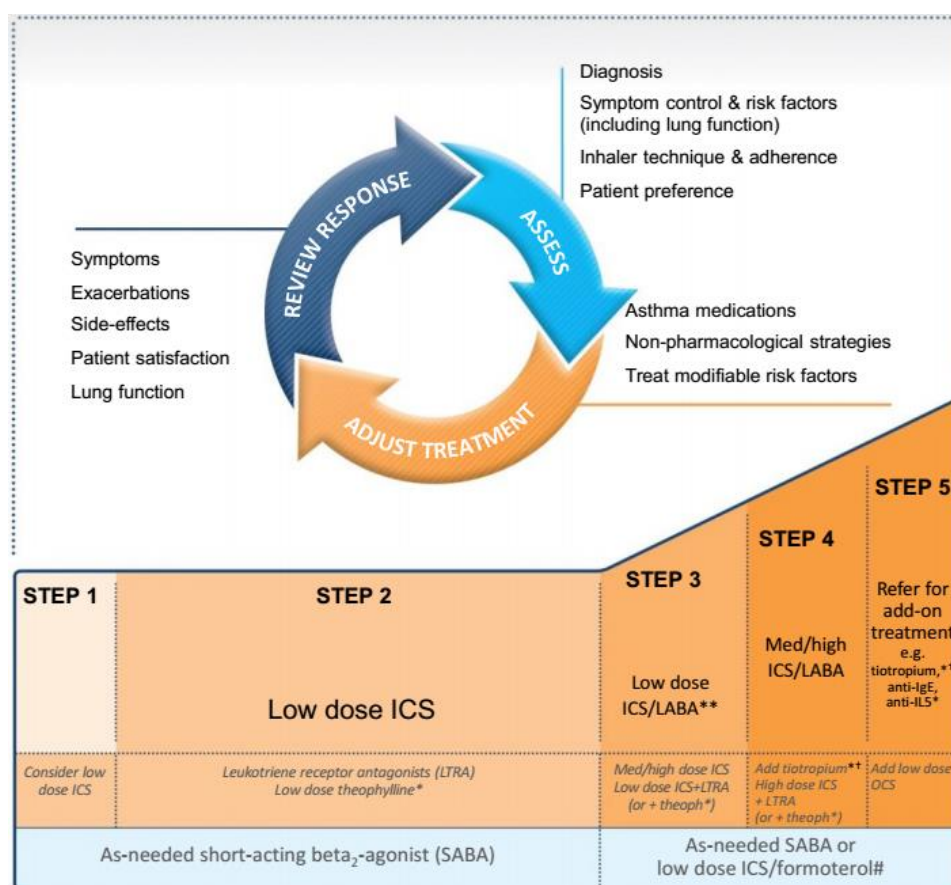


Figure (4): Stepwise management – pharmacotherapy (GINA, 2017).

Step 1: As-needed reliever inhaler:

Preferred option: As-needed inhaler Short-Acting Beta₂-Agonist (SABA). However, there is insufficient evidence about the safety of treating asthma with SABA alone; so, this option should be reserved for patients with occasional daytime symptoms (e.g. less than twice a month) of short duration (a few hours), with no night waking and with normal lung function. More frequent symptoms, or the presence of any exacerbation risk factors such as FEV₁ < 80% personal

best or predicted or an exacerbation in the previous 12 months, indicate that regular controller treatment is needed (*Pauwels et al., 2003*).

Other options: Regular low dose ICS should be considered, in addition to as-needed SABA, for patients at risk of exacerbations (*Pauwels et al., 2003*).

Step 2: Low dose controller medication plus as-needed reliever medication:

Preferred option: Regular low dose ICS plus as-needed SABA. Treatment with ICS at low doses reduces asthma symptoms, increases lung function, improves quality of life, and reduces the risk of exacerbations and asthma-related hospitalizations or death (*Chauhan and Ducharme, 2012*).

Other options: Leukotriene Receptor Antagonists (LTRA) are less effective than ICS. They may be appropriate for initial controller treatment for some patients who are unable or unwilling to use ICS; for patients who experience intolerable side-effects from ICS; or for patients with concomitant allergic rhinitis (*Chauhan and Ducharme, 2012*).

Step 3: One or two controllers plus as-needed reliever medication:

Preferred option (adults/adolescents): Combination low dose ICS/LABA as maintenance treatment plus as-needed SABA or combination low-dose ICS/formoterol (budesonide or

beclometasone) as both maintenance and reliever treatment (*Dahl et al., 2002*).

Preferred option (children 6-11 years): Moderate dose ICS plus as-needed SABA. Before considering a step up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma. In children, the preferred option is to increase ICS to medium dose, and in this age group, the effect may be similar to or more effective than adding LABA (*Dahl et al., 2002*).

Other options: Another option for adults and adolescents is to increase ICS to medium dose, but this is less effective than adding a LABA (*Ducharme et al., 2010*). Other less efficacious options are low dose ICS plus either LTRA or low dose, sustained-release theophylline (*Ducharme et al., 2011*).

Step 4: Two or more controllers plus as-needed reliever medication:

Preferred option (adults/adolescents): Combination low dose ICS / formoterol as maintenance and reliever treatment, **or** combination medium dose ICS/LABA plus as-needed SABA (*GINA, 2017*).

Preferred option (children 6-11 years): Refer to expert assessment and advice. The selection of step 4 treatment depends on the prior selection at step 3. Before stepping up, check for common problems such as incorrect inhaler