
بنام خداوند جان و خرد

Severe Asthma and Novel Biologic Therapies

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Severe Asthma

- Children and young people with severe asthma represent a relatively small proportion of the pediatric asthma population; however, they consume disproportionate resources in terms of treatment costs and hospital admissions.
- Asthma attacks and even asthma deaths occur in children of all severities, suggesting that the seriousness of their asthma was underestimated.
- When a child with poor asthma control is reviewed, it is important to stop and ask three key questions before simply further escalating treatment:

    1. Is this asthma?
    2. Are all the symptoms due to asthma?
    3. Why is asthma control poor?

prevalence of severe asthma

- Estimates of the prevalence of severe asthma vary from 0.2% to 3.2% of the general pediatric population to 2.1%-13% of children with asthma.
- Improvements in the assessment of children with severe asthma, particularly adherence monitoring, suggesting that less than 2.5% of children with asthma have severe asthma.

Definitions

The joint European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines:

It is defined in three parts:

firstly, the diagnosis of asthma must be confirmed with objective tests;

secondly, prescription of high-dose ICS, as defined by the Global Initiative for Asthma (GINA), plus at least one other controller (LABA, leukotriene receptor antagonist [LRTA] or theophylline) or maintenance oral corticosteroids (OCS) for at least 50% of the preceding year;

and thirdly, despite high dose treatment and once modifiable factors have been addressed, control remains poor or becomes uncontrolled once treatment is stepped down.

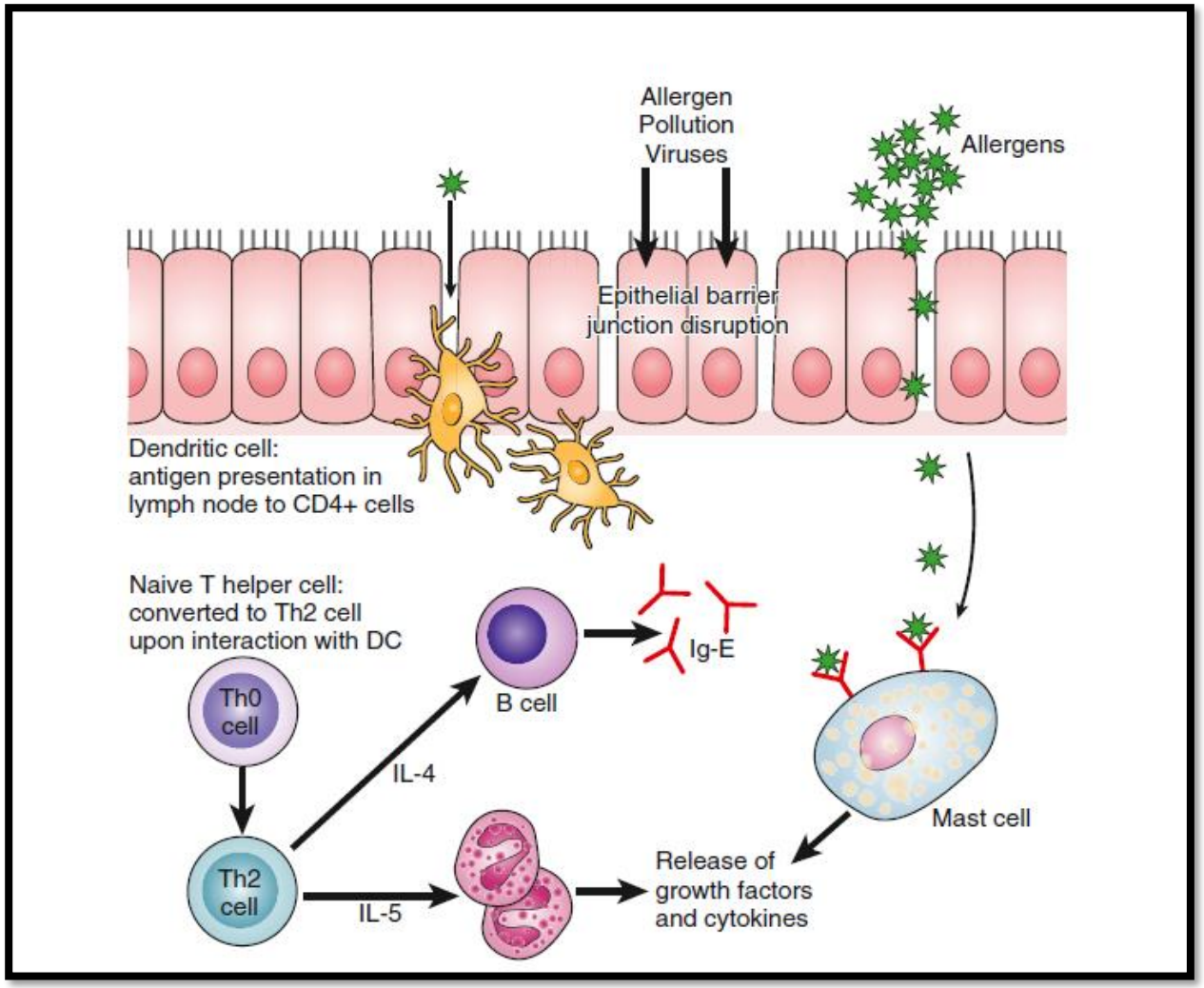
TABLE 37.1 Definitions of High-Dose Inhaled Corticosteroids

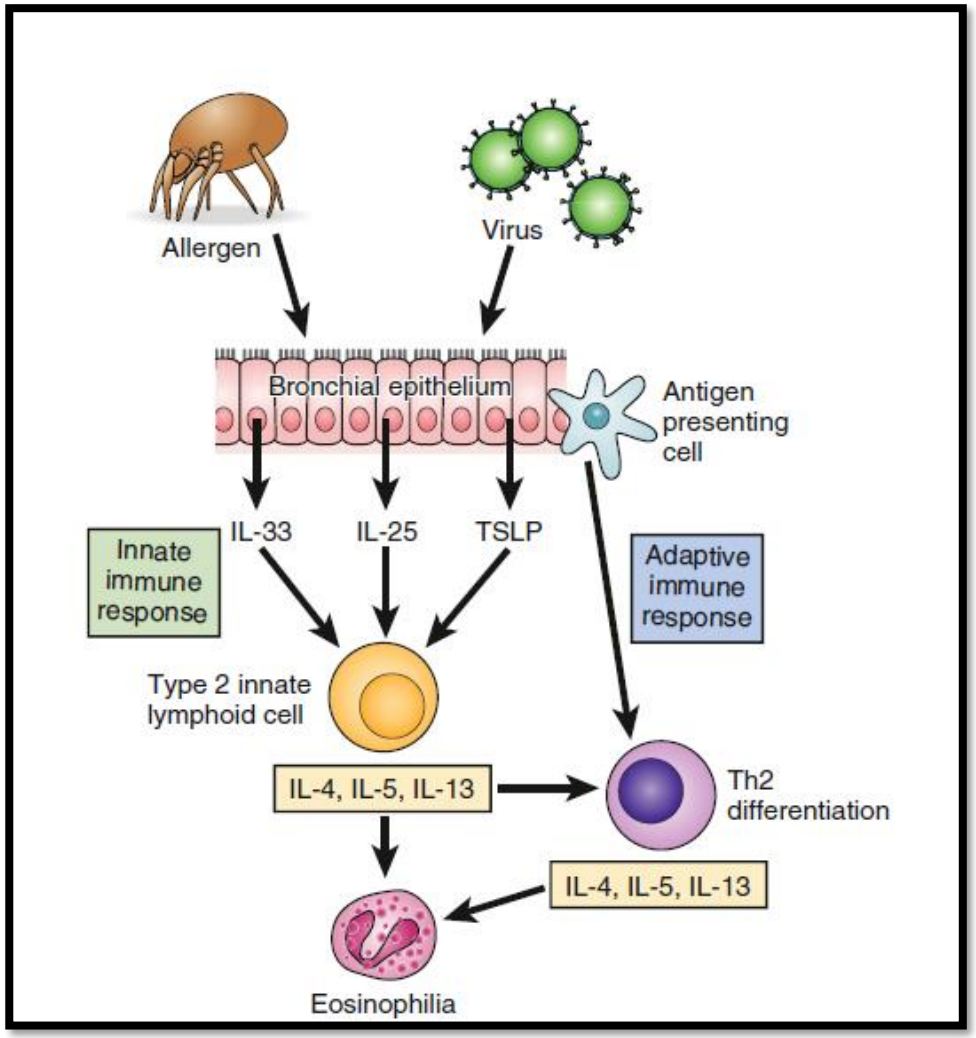
Inhaled Corticosteroid	TOTAL DAILY ICS DOSE (mcg)	
	Adolescents (≥12 Years)	Children Aged 6–11 Years
Beclomethasone dipropionate	>1000	>400
Beclomethasone dipropionate (extrafine particle)	>400	>200
Budesonide	>800	>400
Ciclesonide (extrafine particle)	>320	>160
Fluticasone furoate	200	N/A
Fluticasone propionate	>500	>200
Mometasone furoate	>400	200

Pathophysiology of Severe Asthma

Heterogeneity of asthma phenotypes/endotypes:

- Type 2 high: eosinophilic, IgE-driven, allergic.
- Type 2 low: neutrophilic, paucigranulocytic, harder to treat.
- Key inflammatory pathways (IL-4, IL-5, IL-13, IgE).


Allergen
Pollution
Viruses
Allergens
Epithelial barrier
junction disruption
Dendritic cell:
antigen presentation in
lymph node to CD4+ cells
Naive T helper cell:
converted to Th2 cell
upon interaction with DC
Th0
cell
B cell
Ig-E
IL-4
Th2
cell
IL-5
Mast cell
Release of
growth factors
and cytokines


Allergen
Virus
Bronchial epithelium
Antigen
presenting
cell
IL-33
IL-25
TSLP
Innate
immune
response
Adaptive
immune
response
Type 2 innate
lymphoid cell
IL-4, IL-5, IL-13
Th2
differentiation
IL-4, IL-5, IL-13
Eosinophilia

Asthma Control

- **uncontrolled asthma**

GINA defines uncontrolled asthma as one or both of the following:

1)Poor symptom control (frequent daytime symptoms more than twice per week, night waking due to asthma, short-acting beta agonist [SABA] reliever more than twice per week, activity

limitation)

2)A validated symptom score such as the Asthma Control Questionnaire (ACQ) less than 1.5 or the Asthma Control Test (ACT) or childhood ACT (cACT) less than 20 can also be used.

Asthma Control

- **Difficult to Treat or Problematic Severe Asthma**

The umbrella terms difficult to treat asthma (DTA) or problematic severe asthma (PSA) include all those who present with ongoing poor control despite high-intensity treatment before any further assessment has taken place

- **Refractory Difficult Asthma**

A small number of children will continue to have poor control and be at risk of attacks despite the identification of potentially modifiable factors

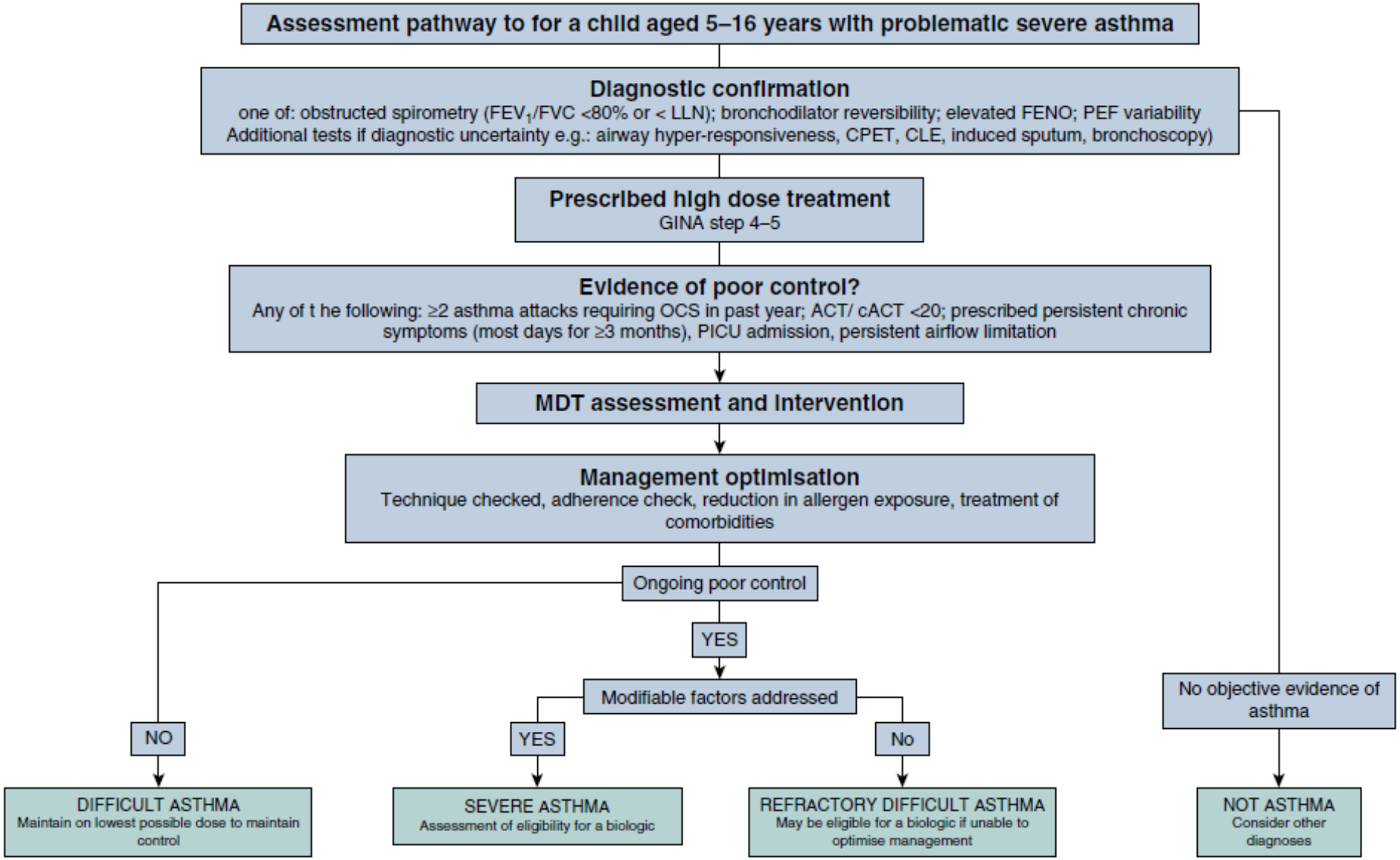


Fig. 37.1 Assessment pathway for children with problematic severe asthma. *ACT,* Asthma control test; *cACT,* childhood ACT; *GINA,* global initiative for asthma; *MDT,* multi-disciplinary team; *OCS,* oral corticosteroids; *PICU,* pediatric intensive care unit.

A Systematic Approach: Three Key Questions

- Is This Asthma?

the importance of objective testing in a child with reported symptoms suggestive of asthma. asthma misdiagnosis in the general pediatric asthma population is common (up to 50% overdiagnosis, and 10% underdiagnosis).

ERS recommended spirometry, bronchodilator reversibility (BDR), and exhaled nitric oxide (FeNO) as first-line diagnostic tests for children.

Even children with severe asthma may have normal spirometry, particularly when well.

FeNO can be normal in children with severe asthma, even in the presence of eosinophilic airway inflammation.

For children with consistently normal lung function, tests of airway hyper-responsiveness (AHR) can be useful. A negative test in children has a high negative predictive Value. A positive test may, however, be seen in normal children.

A Systematic Approach: Three Key Questions

- Are All the Symptoms Due to Asthma?

A number of comorbidities including DB, obesity, rhinitis, anxiety disorders, and depression can mimic or exacerbate asthma symptoms and can negatively impact asthma control and medication adherence.

Dysfunctional breathing (DB) can coexist with or mimic asthma. A variety of terms are used, including breathing pattern disorder, which usually includes abnormalities in breathing pattern and rate (e.g., poor diaphragmatic engagement, apical breathing, hyperventilation, thoraco-abdominal asynchrony), and inducible laryngeal obstruction (ILO), which describes upper airway abnormalities including supraglottic laryngeal obstruction and vocal cord dysfunction

TABLE 37.3 Comorbidities and Management Approached in Children With Asthma

Clinical Trait	Description	Management
Allergic rhinitis	Allergic sensitization and allergic rhinitis common in children (up to 80%)[55]	Antihistamines, nasal steroids
Chronic rhinosinusitis and nasal polyps	Rare in children; nasal polyps suggest an alternative diagnosis such as cystic fibrosis or primary ciliary dyskinesia	Sinus rinses, nasal steroids, surgery
Breathing pattern disorder (BPD); including vocal cord dysfunction (VCD)	One study in children found only 6% of children with severe asthma had BPD; this is likely an underestimate,[56] prevalence of VCD unknown	Physiotherapy for BPD and EILO; speech and language therapy for VCD; surgery for supraglottic EILO in selected cases
Obesity	Children with severe asthma have a higher BMI although few children with severe asthma are clinically obese[57]	Weight loss program; bariatric surgery
Depression and anxiety	High levels of anxiety in both children with severe asthma and their caregivers	Psychological support
Gastroesophageal reflux	Diagnosed in 20% of children with severe asthma, although unrelated to any measures of asthma severity[57,58]	Proton pump inhibitors; little evidence to suggest an impact on asthma symptoms
Obstructive sleep apnea (OSA)	Reported prevalence of 63% in poorly controlled asthma secondary to adeno-tonsillar hypertrophy[59]	CPAP, weight loss, adenotonsillectomy

BMI, Body mass index; *EILO*, exercise-induced laryngeal obstruction.

Adapted with permission from Fleming L, Heaney L. Severe asthma-perspectives from adult and pediatric pulmonology. *Front Pediatr.* 2019;7:389.

A Systematic Approach: Three Key Questions

- **WHY IS ASTHMA CONTROL POOR?**

Most children respond to low-dose ICS, and therefore once the diagnosis of asthma is confirmed it is essential that the reasons for poor treatment response are explored, rather than simply escalating ICS doses and adding in more additional controllers

The most likely explanation: inhalers are not being used regularly and as prescribed, are taken incorrectly

Adherence: Poor adherence to asthma medication is the most important factor contributing to inadequate asthma management and contributes to poor asthma control, asthma attacks, hospitalizations, and deaths.

Inhaler Technique

Allergen Exposure

Smoking and E-Cigarette Use

Socioeconomic Factors

MANAGEMENT OF SEVERE ASTHMA

- Over the past 20 years, there has been a rapid expansion in the availability of targeted biological therapies for severe asthma. For children on high-dose ICS plus LABA for whom a step up in treatment is indicated, consideration should be given to the addition of a biologic in those with evidence of Type 2 high (T2) airway inflammation before other add-on therapies.
- T2 inflammation is characterized by eosinophilic airway inflammation, high blood eosinophils, high FeNO, and atopy and is mediated by the T2 cytokines IL4, 5, and 13.

Omalizumab

- Omalizumab is a recombinant monoclonal antibody to IgE, binds to free IgE, preventing binding to mast cells and basophils, thus inhibiting degranulation and release of proinflammatory cytokines.
- Rout: subcutaneous injection every 2-4 weeks and dosing depends on weight and level of IgE
- biomarker of response: FeNO and blood eosinophils (IgE level, this is a poor biomarker of response)
- good efficacy, particularly in the reduction of attacks
- Can be used seasonally, 4-6 weeks before the start of the new school year

Drugs Targeting IL-5: Mepolizumab, Reslizumab, and Benralizumab

- mepolizumab, reslizumab both bind circulating IL-5, and benralizumab blocks the IL-5 receptor
- Reslizumab is only licensed by the FDA for adults. Blocking IL-5 inhibits eosinophilic maturation and activation

Mepolizumab

- The only anti-IL-5 biologic licensed down to 6 years of age
- Eligibility is based on blood eosinophil count
- subcutaneous injection every 4 weeks, with a lower dose for those less than 12 years
- reduction in attacks
- Steroid-sparing effect in those prescribed OCS
- GINA, recommend consideration of omalizumab and dupilumab ahead of mepolizumab in 6-11 year-olds

Benralizumab

- binds to the IL-5 receptor alpha subunit; inhibiting growth and activation of eosinophils
- binds to the Fc receptor on natural killer cells and induces antibodydependent cell-mediated cytotoxicity leading to apoptosis of eosinophils
- A similar mode of action to mepolizumab, binds to IL-5
- reduction in exacerbations
- No benefit was seen in the 12-17 years old age group, and it is currently only licensed for adults

Dupilumab

- binds to the IL-4 receptor alpha subunit, blocking the signaling of IL-4 and IL-13 and hence the production of IgE by B cells and inhibits the recruitment and activation of eosinophils
- Significant reduction in attacks and improvement in FEV1 within 12 weeks of starting treatment
- steroid-sparing effect was also seen in those prescribed maintenance OCS
- Eligibility is based on evidence of T2 inflammation (blood eosinophils and FeNO)

Tezepelumab

- inhibits thymic stromal lymphopoietin (TSLP), a bronchial epithelial cell-derived alarmin implicated in multiple downstream processes including the regulation of T2 immunity
- Phase III studies demonstrated a significant reduction in severe attacks, the results remained significant even in those without evidence of T2 inflammation (blood eosinophils <150/mL3 or FeNO < 25 ppb), thus suggesting that this upstream mediator affects disease activity more broadly than T2 processes

Dosing & Administration (Quick Reference)

Medication	Dosing Regimen
Omalizumab	≥6y; SC q2–4 wk, weight & IgE-based dosing
Mepolizumab	6–11y: 40mg q4wk; ≥12y: 100mg q4wk
Benralizumab	≥6y; 30mg q4wk ×3 doses → q8wk maintenance
Dupilumab	6–11y: weight-based (q2–4wk); ≥12y per label
Tezepelumab	≥12y; 210mg q4wk