

SEVERE ASTHMA – BIOLOGIC TREATMENT

Asthma is a heterogeneous syndrome with several clinical **phenotypes**. Based on age of onset is classified as childhood vs. adulthood and based on severity is classified in four categories: intermittent, mild persistent, moderate persistent, and severe persistent.

Asthma is also heterogeneous biologically with two major distinct **endotypes** patterns of airway inflammation:

- **Type 2 high-inflammation, eosinophilic** (type 2-high) characterized by eosinophilic airway inflammation which is associated with increased blood eosinophil counts or elevations of fractional exhaled nitric oxide (FENO).
- **Type 2 low-inflammation, non-eosinophilic** (type 2-low) encompasses neutrophilic asthma and paucigranulocytic asthma.

Type 2-high inflammation in asthma is generally suppressed by glucocorticoids, as evidenced by a rapid decrease in FENO when treatment with inhaled glucocorticoids is initiated and an immediate decrease in blood eosinophil counts with the use of oral glucocorticoids.

A group of patients do not respond to standard treatment and develop severe persistent asthma defined as:

- **Severe asthma definition:** persistent symptoms or frequent exacerbations that require repetitive glucocorticoid bursts, maintenance oral glucocorticoid therapy, or both, despite adequate treatment with high-dose inhaled glucocorticoids, long-acting β_2 -agonists, and long-acting muscarinic antagonists.

In patients with severe asthma, biologic therapies are recommended to reduce the disease burden.

There are four groups of biologics (monoclonal antibodies):

- Anti-IgE Antibodies - omalizumab (Xolair)
- Anti-Interleukin-5 and 5R Receptor Antibodies – [Mepolizumab](#), [Reslizumab](#), and [Benralizumab \(Nucala, Cinqair, and Fasenra\)](#)
- Anti-Interleukin-4 Receptor Antibodies – Dupilumab (Dupixent)
- Anti-Epithelial Cytokine Antibodies - TSLP (thymic stromal lymphopoietin) - Tezepelumab (Tezspire)

Severe asthma despite high-dose ICS + LABA and adequate management

- Determine blood eosinophil counts and FENO
- Assess coexisting conditions (e.g., severe atopic dermatitis, CRSWNP, allergic rhinitis, eosinophilic pneumonia, EGPA)

Choice of Antibody Monoclonal treatment of Severe Asthma According to Patient Characteristics

Characteristic	Anti-IgE Antibody	Anti-Interleukin-4R Antibody	Anti-Interleukin-5 or Anti-Interleukin-5R Antibody
Indication	Severe allergic asthma	Severe type 2 asthma	Severe eosinophilic asthma
Age group	Children, adolescents, and young adults	Children, adolescents, and adults	Adults
Onset	Childhood	Childhood or adulthood	Adulthood
Allergy	Prerequisite: IgE sensitization to perennial allergen	Irrespective of allergy	Irrespective of allergy
Dominant biomarker	Serum total IgE (for dosing)	Increased FENO	Increased blood eosinophil count
Serum total IgE	Serum total IgE and weight within dose range, according to local eligibility criteria	Irrespective of total IgE	Irrespective of total IgE
Blood eosinophil count [†]	Slightly better response with increased count	>150 to <1500/ μ l [†]	Prerequisite: increased counts (according to local eligibility criteria), >150 to 300/ μ l [†]
FENO [†]	Slightly better response if increased FENO	Better response if FENO >25 ppb	Irrespective of FENO
Coexisting conditions	Allergic rhinitis, CRS with nasal polyposis, chronic urticaria	Atopic dermatitis, CRS with nasal polyposis	CRS with nasal polyposis
Exacerbations in previous yr	According to local criteria	According to local criteria	High frequency (\geq 2), as specified by local criteria

* In December 2021, the anti-TSLP antibody tezepelumab was approved by the FDA for the add-on maintenance treatment of adults and pediatric patients 12 years of age or older who have severe asthma, with no phenotype (e.g., allergic or eosinophilic) or biomarker limitation within its approved label (Fig. S2 in the Supplementary Appendix). FENO denotes fractional exhaled nitric oxide, and ppb parts per billion.

[†] Blood eosinophil counts and FENO values are for patients with severe asthma who are not receiving maintenance oral glucocorticoid therapy.

