# Add-on Type 2-targeted biologic therapy for severe allergic/eosinophilic asthma

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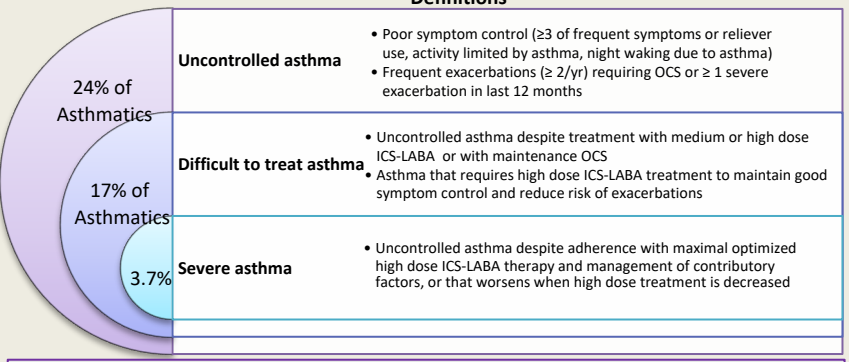
## Definitions

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| **Uncontrolled asthma** | • Poor symptom control (≥3 of frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)<br>• Frequent exacerbations (≥ 2/yr) requiring OCS or ≥ 1 severe exacerbation in last 12 months |
| **Difficult to treat asthma** | • Uncontrolled asthma despite treatment with medium or high dose ICS-LABA or with maintenance OCS<br>• Asthma that requires high dose ICS-LABA treatment to maintain good symptom control and reduce risk of exacerbations |
| **Severe asthma** | • Uncontrolled asthma despite adherence with maximal optimized high dose ICS-LABA therapy and management of contributory factors, or that worsens when high dose treatment is decreased |

## Assessment of severe asthma phenotype

- Assess factors contributing to symptoms, quality of life, and exacerbations
- Assess the severe asthma phenotype during high dose ICS treatment (or lowest possible dose of OCS)
- Investigate for comorbidities/differential diagnoses and treat as appropriate
  - Consider: FBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) guided by clinical picture

## Does patient have features suggestive of type 2 airway inflammation

- Blood eosinophils **≥150/µl** and/or
- FeNO **≥20 ppb** and/or
- Sputum eosinophils **2%** and/or
- Asthma is clinically **allergen –driven** and/or
- Need for maintenance **oral corticosteroids** (OCS)

(Repeat peripheral eosinophils up to 3X, on lowest possible corticosteroids)

**Patient likely to have residual type 2 airway inflammation**

- Consider adherence, increasing ICS dose for 3-6 months, and co-morbidities with specific add-on treatment (AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis)

**THEN**

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local hospital policy, eligibility criteria, co-morbidities** and **predictors of response**, as well as cost, dosing frequency, route (SC or IV), patient preference when choosing between available therapies

## Add-on anti-IgE for severe allergic asthma

**Omalizumab** is approved as add-on therapy for age ≥ 6 years in patients with severe allergic asthma, given by SC injections every 2-4 weeks, with dose based on weight and serum IgE. Suggested initial trial at least 4 months.

**Mechanism;** binds to Fc region of free IgE, preventing IgE binding to FcεRI receptors, reducing free IgE and down regulating receptor expression.

**Eligibility criteria;** ***review local institution eligibility criteria***

- Positive skin test or *in vitro* reactivity to a perennial aeroallergen
- Total serum IgE and body weight within local dosing range (patients with baseline IgE lower than 76 IU/ml were less likely to experience benefit)
- Multiple documented severe asthma exacerbations despite daily high-dose ICS-LABA

**Benefits:**

- RCTs in severe allergic asthma showed 34% decrease in severe exacerbations, but no significant difference in symptoms or quality of life.
- Open label studies in patients with severe allergic asthma and ≥ 1 severe exacerbation in last 12 mo, there was 50-65% reduction in exacerbation rate, significant improvement in quality of live and 40-50% reduction in OCS dose.

**Potential predictors of response:**

- One observational study showed greater decrease in exacerbations if blood eosinophils ≥260/µl, or FeNO ≥20 ppb
- Childhood-onset asthma.
- Clinical history suggesting allergen-driven asthma.
- Baseline IgE level doesn't predict likelihood of response.

**Potential adverse events;** injections site reaction, anaphylaxis in 0.2%.

## Add-on Anti-IL5 / Anti-IL5R for severe eosinophilic asthma

**Currently Approved Anti-IL5 / Anti-IL5R for ages ≥ 12 yrs: Mepolizumab** (Anti-IL5), 100mg given by SC injection every 4 weeks. **Benralizumab** (anti-IL5 receptor α subunit), 30 mg given by SC injection 4-weekly for 3 doses then 8-weekly. **Currently Approved Anti-IL5 for ages ≥ 18 yrs: Reslizumab** given by IV infusion 3mg/kg 4-weekly. Suggested initial trial at least 4 months.

**Mechanism;** Interleukin-5 [IL-5] is a major regulator of eosinophilopoeisis, and eosinophil survival and activity in tissues. Benralizumab binds to IL-5 receptor α subunit leading to apoptosis of eosinophils. Mepolizumab and Reslizumab bind circulating IL-5, thereby blocking its biological effects.

**Eligibility criteria;** ***review local institution eligibility criteria for each product***

- Multiple documented severe asthma exacerbations in the last year despite high dose ICS-LABA
- Blood eosinophils above locally specified level (eg ≥150 or ≥ 300/µl; a different threshold may apply for patients on OCS)

**Benefits:**

- RCTs in severe asthma patients with exacerbations in last year, with varying eosinophil criteria, showed anti-IL5 and anti-IL5R therapy reduced severe exacerbations by ~ 55%, and improved quality of life, lung function and symptom control
- RCTs in patients taking OCS showed mepolizumab or benralizumab treatment allowed a ~ 50% reduction in median OCS dose compared to placebo
- All anti IL5 therapies reduced blood eosinophils, with almost complete suppression with benralizumab

**Potential predictors of response:**

- Higher blood eosinophils (strong predictor)
- Higher number of severe exacerbations in previous year (strongly predictive)
- Adult-onset asthma
- Nasal polyposis
- Maintenance OCS at baseline

**Potential adverse events;** injections site reaction, anaphylaxis is rare. Adverse events generally similar between active and placebo groups in RCTs

Reference; Global initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from; www.ginasthma.org