GINA steps for the treatment of those with difficult-to-treat and severe asthma

Global Initiative for Asthma (GINA). Available at www.ginasthma.org/reports.

Step 1: Providers should confirm the diagnosis of difficult-to-treat asthma. Patients should be referred to a specialist or severe asthma clinic at any stage, but particularly if:

- There is difficulty confirming an asthma diagnosis
- Patient has frequent urgent healthcare use
- Patient requires frequent oral corticosteroid bursts, or maintenance oral corticosteroids
- Occupational asthma is suspected
- Patient has concomitant food allergies or history of anaphylaxis
- Symptoms suggest an infection or cardiac cause
- Symptoms are possible bronchiectasis
- Patient presents with multiple comorbidities

Providers should also recognize that persistent airflow limitation (non-reversible FEV_1) may occur with long-standing asthma due to airway remodeling or limited lung development in childhood.

Step 2: Healthcare providers are advised to assess for contributing factors that could be contributing to uncontrolled symptoms, worsening exacerbations, or poor quality of life. Most important modifiable factors are:

- Incorrect pulmonary device technique
- Poor adherence
- Comorbidities including anxiety/depression, obesity, deconditioning, chronic rhinosinusitis, inducible laryngeal obstruction, GERD, COPD, sleep apnea, bronchiectasis, cardiac disease, and kyphosis due to osteoporosis
- Modifiable risk factors and triggers including smoking, second-hand smoke exposure, allergen exposure, indoor and outdoor air pollution, molds and noxious chemicals, and medications like beta blockers and NSAIDS.
- Regular or overuse of SABA rescue inhalers
- Medication side effects

Step 3: Optimize treatment plans by providing asthma self-management education, confirm patients have a written action plan, optimize inhaled controller regimens, treat comorbidities and modifiable risk factors, consider non-pharmacologic add-on therapy (e.g., smoking cessation, lifestyle modifications, mucus clearance strategies, influenza vaccination, breathing exercises, allergen avoidance), consider a trial of non-biologic medication such as tiotropium or montelukast (if not already using), and consider a trial of high dose ICS (if not already using).

Step 4: Review the response to above steps 1-3 interventions after 3-6 months. The timing will depend on the clinical urgency as well as what changes were implemented. When assessing response to treatment, a review of symptom control, exacerbation history, medication side effects, inhaler technique and adherence, lung function, and patient satisfaction should be assessed. **If asthma is still uncontrolled**, this confirms the diagnosis of severe asthma and patient should be referred to a specialist or severe asthma clinic (if not previously done). **If asthma is controlled**, consider stepping down treatment by starting with a reduction or discontinuation of oral corticosteroids, then remove other

add-on therapies. However, **if asthma becomes uncontrolled when treatment is stepped down**, the diagnosis of severe asthma has been confirmed and patient should resume previous therapy and be referred to a specialist (if not already). **If patient remains well-controlled** after stepping down treatment, the patient does not have severe asthma and their asthma management should continue to be optimized.

Step 5: Assessment and workup at this stage should be by a specialist. Assessment should include:

- Inflammatory phenotype (T2 or non-T2)
- Detailed assessment of comorbidities and differential diagnoses
- Need for social and/or psychological support
- Invite patient to enroll in a registry (if available) or clinical trial (if appropriate)

Patients with T2 inflammation are approximated to include 50% of people with severe asthma. These patients are relatively refractory to high-dose ICS and may find better results with maintenance oral corticosteroids. Type 2 inflammation can be considered refractory when biomarkers (e.g., blood eosinophils ≥150 µl, and/or FeNO ≥20 ppb, and/or sputum eosinophils ≥2% and/or asthma is clinically allergen driven) while on high-dose ICS or daily oral corticosteroids are found. The specialist will consider additional testing.

Step 6a: This step is divided into two parts. When there is no evidence of T2 inflammation, the specialist should review the asthma management basics, recommend avoiding relevant exposures (like tobacco smoke and allergens), consider additional diagnostic investigations (like chest CT), consider a trial of a non-biologic add-on treatment (such as tiotropium or leukotriene modifier), and consider bronchial thermoplasty. There are no biologic options for patients with non-type 2 severe asthma.

Step 6b: This step gives guidance to add-on a biologic for those with T2 severe asthma with exacerbations or poor symptom control while on at least high dose ICS/LABA therapy, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids.

Eligibility criteria for payers, predictors of response (e.g., childhood-onset asthma, clinical history suggesting allergen-driven symptoms, blood eosinophils greater or equal to 260 cells/ µl or FeNO ≥20 ppb, baseline IgE level does not predict likelihood of response), cost, dosing frequency, route and patient preference are considered before selecting therapy. Guidance is provided for selection between anti-IgE, anti-IL-5/anti-IL-5R, and anti-IL-4R. If the patient is not eligible for any therapy, move to step 6a. If patient is eligible, therapy should be trialed for at least 4 months. If the patient response is positive, move to step 7 or possibly extend the trial 6-12 months. If response is not positive or minimal, the specialist can consider switching to a different therapy if eligible and move to step 7.

Step 7: This step is also divided into two parts. When reviewing the patient response, patients with a **positive response** should be re-evaluated every 3-6 months. If step down is indicated, specialists should consider decreasing or stopping the oral corticosteroids first and then other add-on medications. Inhaled therapy can also be decreased, but patients should continue at least a medium dose of ICS. Biologic treatment can be reduced based on observed benefit versus risk. Generally, if a patient responds to a biologic agent, it should not be withdrawn until at least 12 months of treatment, and only if asthma remains well controlled on medium dose ICS therapy. If the patient **response is minimal or not positive**, the biologic should be stopped and the patient should be reassessed and additional testing or treatment may be considered (e.g., high resolution CT, add-on macrolide (off-label), bronchoscopy, etc.).

Step 8: Continue to optimize management including two-way communication with general practice provider for ongoing care. Patients should continue to be seen for follow-up every 3-6 months.