Severe Asthma Roadmap for Improved Diagnosis and Personalized Treatment

– A Guided Workflow

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A — DOES THE PATIENT HAVE ASTHMA?

- **Confirm** variable airflow limitation: review/repeat pulmonary function tests with bronchodilator
- **Consider** methacholine or exercise challenge tests if spirometry inconclusive and clinical response to treatment is absent or limited
- **Exclude** other conditions (eg, airway tumor, foreign body, COPD, bronchiectasis, vocal cord dysfunction, CF, aspiration)

Treat other pulmonary conditions if misdiagnosed

YES — NO

B — AN ASTHMA DIAGNOSIS IS CONFIRMED

1 Asthma education and health maintenance
- Educational action plan
- Self-management plan
- Vaccination
- Smoking cessation
- Healthy lifestyle (diet, exercise, sleep)

2 Identify patient-related factors
- Disabilities, age, poor general health
- Poor health literacy
- Lack of access to health care
- Inability to afford medication

3 Diagnose and manage comorbidities
- Rhinosinusitis/nasal polyps
- Gastroesophageal reflux
- Obstructive sleep apnea
- Vocal cord dysfunction
- Allergic bronchopulmonary aspergillosis
- Eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome)
- Obesity
- Psychological factors (personality, depression, anxiety)
- Drug side effects: aspirin, NSAIDs, beta-blockers, ACE inhibitors
- Aspiration

4 Address environmental factors
- Allergen exposures (indoor, outdoor, pets)
- Occupational exposures
- Respiratory infections (eg, viruses)
- Second-hand cigarette smoke
- Traffic-related pollution
- Respiratory irritants

5 Optimize inhaled therapy
- Choose best device for patient
- Check inhaler technique frequently
- Correct patient's inhaler technique

6 Maximize adherence and minimize side effects
- Assess knowledge and attitudes about medication
- Assess barriers to proper medication use
- Acknowledge patient beliefs about medications
- Teach ways to improve adherence
- Ask and educate about possible side effects
- Use strategies to reduce side effects (eg, spacers for MDIs)

C — IS ASTHMA UNCONTROLLED, DESPITE STEPPING UP TO A HIGH-DOSE ICS + LABA?

- Poor symptom control (ACQ > 1.5, ACT < 20, or per GINA/NAEPP guidelines)
- ≥ 2 bursts of systemic corticosteroids for asthma exacerbations in the past year
- ≥ 1 hospitalization for asthma in the past year
- FEV1 < 80% predicted when not taking short- or long-acting bronchodilators
- Asthma is uncontrolled when any 1 of the 4 criteria above is present - consider referral to asthma specialist

NO — YES

Close follow-up.
Reduce treatment intensity after at least 3–6 months of stable, good control, per GINA/NAEPP guidelines

Consider adding a non-biologic therapy
- Tiotropium
- Leukotriene modifier
- Theophylline
- Macrolide antibiotic
- Oral glucocorticoid (short course)

D — IS ASTHMA STILL UNCONTROLLED, DESPITE TREATMENT WITH HIGH-DOSE ICS + LABA AND A NON-BIOLOGIC ADD-ON THERAPY?

NO — YES

Refer patient to an asthma specialist

E — DETERMINE INFLAMMATORY PHENOTYPE/ ENDOTYPE

- Start with non-invasive testing (allergy testing, IgE level, blood eosinophil count and FENO level)
- If poor response to therapy continues, consider induced sputum differential for eosinophil and neutrophil counts and/or bronchoscopy with endobronchial biopsy and BAL

See Table for Description of Phenotype

SEVERE ASTHMA: INFLAMMATORY PHENOTYPES AND TREATMENT APPROACHES

Inflammatory Phenotype		Common Clinical Features	Biomarkers in Patients Receiving High-Dose ICS	Add-on Pharmacologic Maintenance Therapies	Additional Strategies to Consider*
Type 2 (Th2) inflammation	**IL-4, IL-5, IL-13 mediated inflammation with high eosinophils or FENO**	• Early onset, allergic, with elevated IgE level • Later onset, obesity, female sex, variable airflow obstruction • Exacerbations • Nasal polyps	• Blood eosinophil count ≥ 300/μL • FENO ≥ 20 ppb • Sputum eosinophils ≥ 2%	**Anti–IgE** • Omalizumab (If IgE = 30-700 IU/mL and IgE-mediated hypersensitivity to a perennial allergen) **Anti–IL-5** • Mepolizumab • Reslizumab **Anti–IL-5Rα** • Benralizumab **Anti–IL-4Rα** • Dupilumab	• Maximize treatment of coexisting conditions associated with Th2 inflammation (eg, rhinosinusitis, AERD, ABPA)
Non-Type 2 inflammation	**Neutrophilic airway inflammation**	• Poor response to ICS • Purulent sputum • Bronchiectasis • Low lung function	• Sputum PMNs ≥ 40–60%	• No phenotype-specific treatment currently available • Treat infections • Consider macrolide antibiotics	• Address exposures (smoke, irritants, pollutants) and altered microbiome • Mucus-clearance strategies • Consider Bronchial Thermoplasty
	Paucigranulocytic (noninflammatory) asthma	• Fixed or variable airflow obstruction	• No Th2 biomarkers and sputum PMNs ≤ 40–60%	• No phenotype-specific treatment currently available	• Nonpharmacologic strategies (including pulmonary rehabilitation) • Consider Bronchial Thermoplasty
Possible Th2 inflammation	**Mixed eosinophilic and neutrophilic inflammation**	• Features of both eosinophilic and neutrophilic airway inflammation	• Th2 and neutrophilic markers	• Trial of macrolide antibiotics† for 3–6 months	• Maximize treatment of coexisting conditions associated with Th2 and non-Th2 inflammation (eg, rhinosinusitis, infections)

*Assumes that alternative diagnoses have been excluded, comorbidities have been identified and managed, patient-related factors and environmental exposures have been addressed, inhaled therapy and adherence have been optimized, and non-biologic therapy has been considered or tried (see Roadmap for details).

Abbreviations: **ABPA**, allergic bronchopulmonary aspergillosis; **AERD**, aspirin-related respiratory disease; **FENO,** fractional nitric oxide concentration in exhaled breath; **ICS**, inhaled corticosteroid; **IgE**, immunoglobulin E; **IL**, interleukin; **PMN**, polymorphonuclear leukocyte; **Th2**, T-helper 2.

References

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