The Evaluation of Severe Asthma

Our Approach

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Disclosures of Conflicts of Interest

None

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GINA Definitions

Uncontrolled asthma: one or both of the following:

- Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, nighttime awakening due to asthma)
- Frequent exacerbations (≥2/year) requiring OCS, or serious exacerbations (≥1/year) requiring hospitalization.
- Can become well controlled, if treated properly

GINA Definitions

Difficult-to-treat asthma:

- Uncontrolled asthma despite medium or high dose ICS-containing treatment
- Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities, SABA over-use and other risk factors

Severe asthma:

- Uncontrolled despite adherence to optimized therapy *AND* management of contributory factors or it worsens when high dose treatment is decreased
- Relatively refractory to corticosteroids

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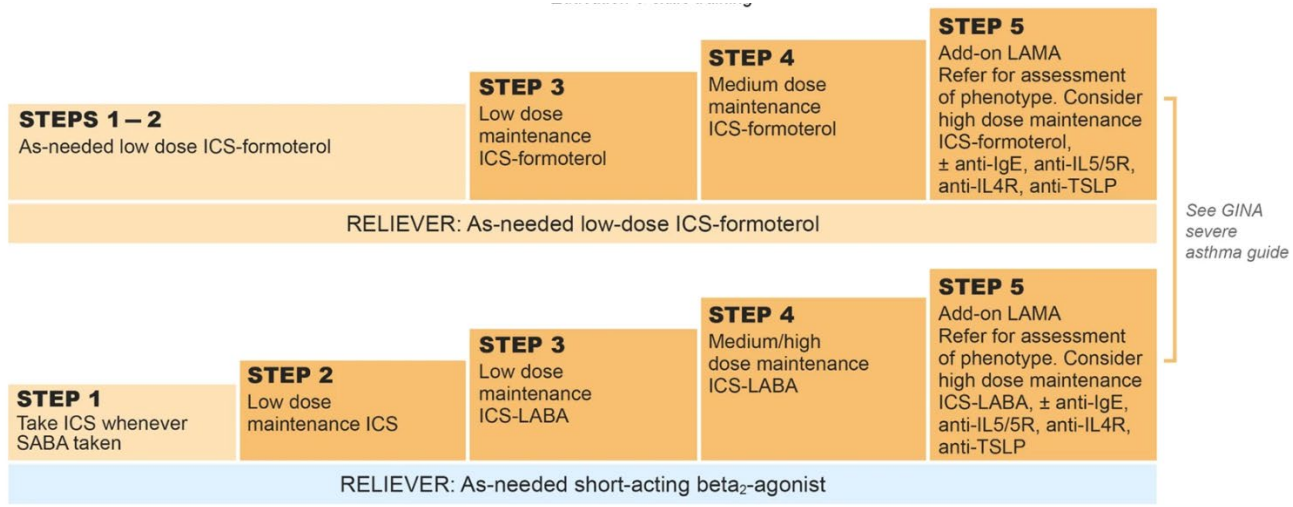
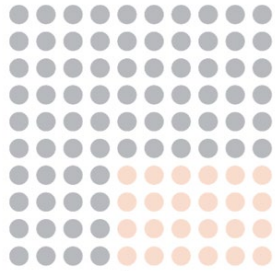
Proportion of Adults with Severe Asthma





24%

GINA Step 4-5 treatment

17%

difficult-to-treat asthma

= GINA Step 4-5 treatment
+ poor symptom control

3.7%

severe asthma

= GINA Step 4-5 treatment
+ poor symptom control
+ good adherence and inhaler technique

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Investigation of Difficult to Treat Asthma

GINA 2025
Severe Asthma Guide

1. Confirm the diagnosis of asthma
2. Look for modifiable factors contributing to symptoms, exacerbations, and poor quality of life
3. Optimize management and review the response to therapy
4. Assess asthma phenotype/endotype and candidacy for biologics
5. Determine whether a patient is ‘high risk’ for exacerbations or other morbidity

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Case 1

History

- 65 year-old woman with life-long allergies and asthma
- history of steroid-dependence
- history of multiple hospitalizations
- resolved with moving off of her horse farm

- Referred by her PCP for 2 years of recurrent asthma despite her ICS/LABA/LAMA, Singulair, and Prednisone
- She had daily wheeze, cough, congestion

Case 1

History

- She had multiple steroid-induced complications: weight gain, hypertension, and diabetes

- She retired from the day to day running of her farm to further distance herself from the horses

Case 1

Past Medical History

- Allergic rhinitis
- Asthma
- Rheumatoid arthritis
- SVT s/p ablation

Meds

- fluticasone furoate/umeclidinium/vilanterol
- montelukast 10 mg
- prednisone 20 mg daily

Exam

- loud expiratory wheezes
- best heard over the anterior chest

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Case 1

Spirometry

- FEV1/FVC ratio: 62%
- FEV1: 1.42, 56% → no reversibility

Exhaled NO

- 8 ppb

CXR

- normal

A diagnostic study was performed……

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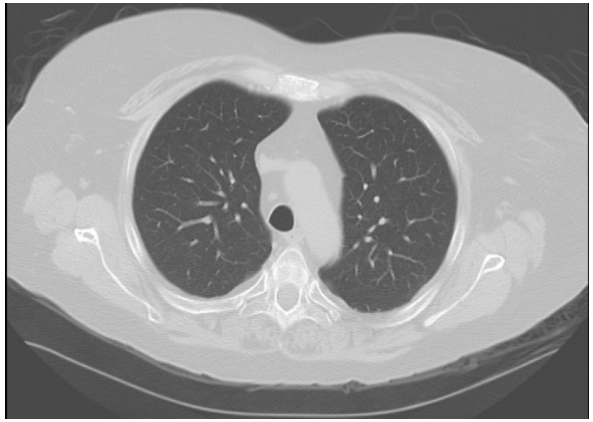
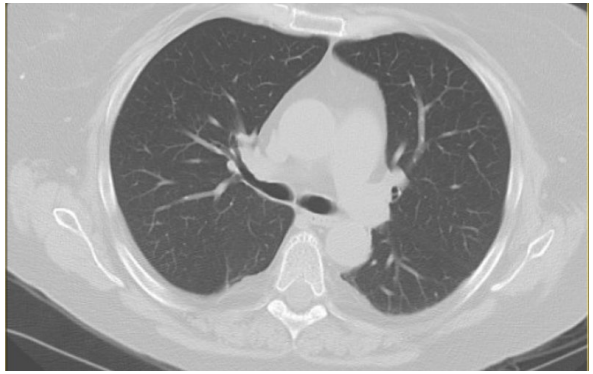
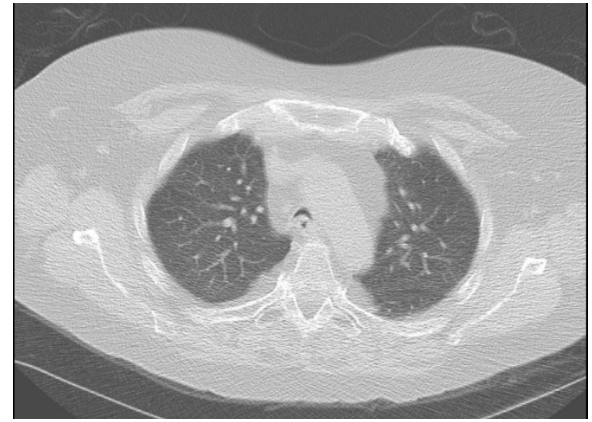
Case 1

Inhalation





Exhalation



Tracheobronchomalacia

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Case 2

History

- 64 yo man referred for chronic chest congestion
- 2 years of increasing DOE, cough, and wheeze

- Lifelong asthma
- 2-3 rounds of OCS for asthma/year associated with colds
- chronic rhinosinusitis with polyposis 7 years ago and has required recurrent surgeries

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Case 2

Past Medical History

- Asthma with fixed airflow obstruction
- CRSwNP
- Progressive hearing loss bilaterally

Medications

- Fluticasone/Salmeterol
- Montelukast
- Tiotropium

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Case 2

Physical Exam

- Nasal polyposis. Bilateral TM perforations.
- Increased AP diameter, bronchial breath sounds

Spirometry

- FEV1/FVC: 55%
- FEV1 = 62%
- No reversibility to bronchodilator

Labs

Absolute Eo Count: 1,500

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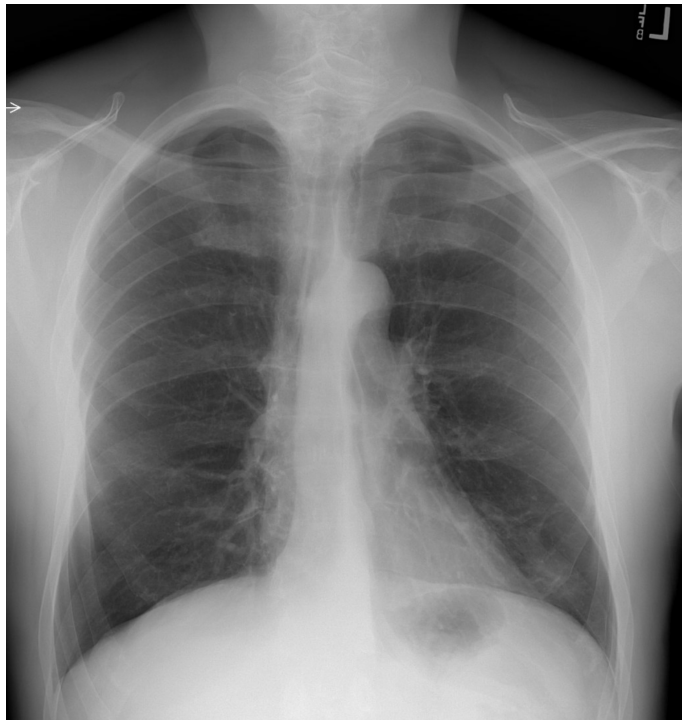
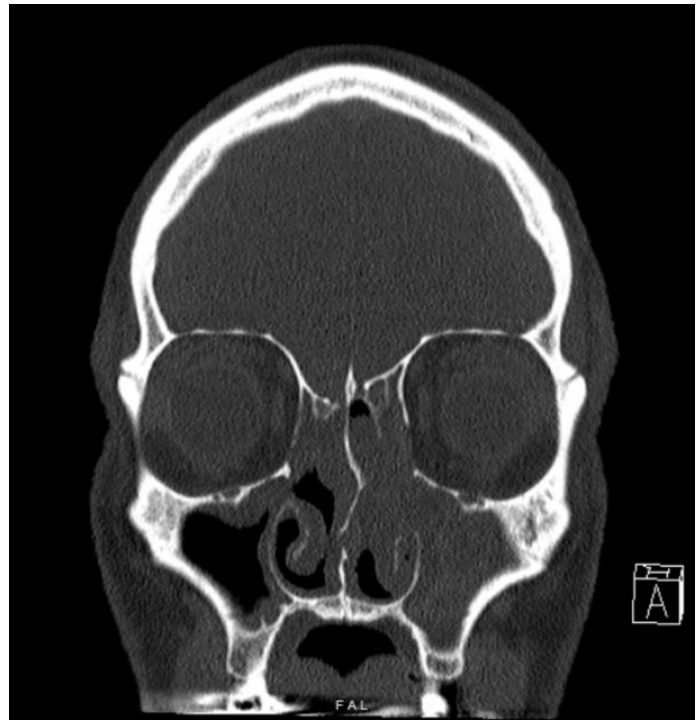
Case 2

CXR: flattened diaphragms



Sinus CT: Extensive Polyposis



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Case 2

Pathology

- Severe acute and chronic polypoid rhinosinusitis with focal seromucinous gland destruction and destruction of small vessels.

Anti-MPO

- 339

Eosinophilic Granulomatosis with Polyangiitis

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Differential Diagnosis

Upper airway
- Inducible laryngeal obstruction
- Upper airway cough syndrome
- Foreign body, tumor, stricture

Primary bronchial disorder
- Bronchiectasis
- Tracheobronchomalacia
- COPD

Genetic disorders
- Cystic fibrosis
- Primary Ciliary Dyskinesia
- Alpha-1 Antitrypsin

'Asthma Plus'
- Wegeners and EGPA
- ABPA

Interstitial Lung Disease w OVD
- Sarcoidosis
- Bronchiolitis

Other
- PE / Pulm hypertension
- Cardiac disease, CHF
- Aspiration, GERD

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Initial Diagnostic Evaluation

History and physical are still paramount!

- SOB/chest tightness vs cough/phlegm vs DOE
- Temporal nature (night?, seasonal?, with cold air?) and response to medications
- Early onset? Childhood eczema? Family history of asthma?
- Late onset? Occupational sx? AERD? Polyposis? Obese?
- Cigarette smoking, vaping, other inhalants?

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Initial Diagnostic Evaluation

- Spirometry with bronchodilator
  - If negative, repeat after weaning medications or when symptomatic
- Chest X-ray / Chest CT scan
- Peripheral blood eosinophils (AEC > 150 cells/uL)
  - If AEC ≥ 300 cells/ul consider Strongyloides
  - If AEC ≥ 1500 cells/ul consider EGPA
- Exhaled nitric oxide
- Allergy testing: IgE, RAST or skin test
- Sputum analysis
  - cell counts with eos ≥ 2%
  - gram stain, culture

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Specialized Testing

Limited reversibility to bronchodilator or abnl CXR

Chest CT

- Emphysema
- Bronchiectasis
- Malacia (dynamic airway imaging)

Genetic testing

- Alpha 1 AT
- CF and PCD

Bronchoscopy

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Specialized Testing

Prominent sinonasal congestion

- Sinus CT, ENT examination
- CF and PCD testing
- Allergy testing
- Aspirin challenge
- GERD evaluation

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Specialized Testing

Chronic chest congestion or recurrent infiltrates

- pH probe and manometry
- Speech and swallow
- Immunoglobulins
- ANCAs
- Total IgE and RAST to Aspergillus

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Specialized Testing

Dry cough/exercise-induced sx w/ normal spiro
(after exclusion of other cardiopulmonary disease)

- Inducible laryngeal obstruction assessment
- Methacholine
- Bronchoprovocation challenge
  - dry-air exercise challenge
  - +/- direct laryngoscopy

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Inhaler technique and non-adherence

Frequency

- Incorrect inhaler technique seen in up to 80% of patients
- Suboptimal adherence in up to 75%

Obstacles to regular use

- Misunderstanding of instructions
- Costs
- Concerns about complications and dependence
- Depression
- Can they identify when to take it?

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Co-Morbidities/Aggravating Factors

- Environmental
  - pets, pests, smoke
  - pollution, industrial/occupational exposures
- Food Allergy, Chronic Rhinosinusitis +/- Polyposis
- Gastroesophageal reflux
- Obesity or T2 diabetes
- Medications: beta-blockers
- Smoking, vaping, marijuana, drug use
- Immune deficiency
- Chrohns, rheumatoid arthritis

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Evaluation of Co-Morbidities with Validated Questionaires

1. Dysfunctional Breathing / Hyperventilation (Nijmegen score)
   - J Asthma 2014; 51:839-46.
2. VCD (Pittsburgh VCD index)
   - Traister RS, et al. JACI In Practice 2014; 2:65-9.
3. OSA (Berlin questionnaire)
   - Netzer NC, et al. Ann Intern Med 1999; 131:485-91.
4. GERD questionnaire
   - Jonasson C, et al. Alimentary pharmacology and Therapeutics 2013; 37:564-72.
5. Hospital Anxiety and Depression score
   - J Psychosomatic Research 2002; 52:69-77.
6. Allergic Rhinitis (SFAR)
   - Allergy 2002; 57:107-14.
7. Sinonasal disease
   - Chest 2009; 136:1324-32.

Optimize Management of Co-morbidities

1. Optimize Asthma Meds
    1. MART
    2. Leukotriene antagonism
    3. Anti-cholinergics
    4. Short-term high dose ICS/LABA
2. Asthma Self Management Plan
3. Non-pharmacologic therapies
    1. Smoking Cessation
    2. Weight loss, Exercise
    3. Mucus clearance
    4. Allergen avoidance, address respiratory viruses
    5. Routine vaccinations – pneumonia, RSV, yearly flu, yearly covid
    6. Anxiety, Depression

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Asthma Endotypes

Endotype: subtype defined by a distinct pathophysiologic mechanism

- Immune endotypes
- Epithelial phenotypes
- Metabolic
- Neurologic
- Genetic

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Asthma Endotypes

T2 High Asthma

- Allergic asthma
- Aspirin-sensitive asthma
- ABPA / EGPA
- Severe late-onset hypereosinophilic

Paucigranulocytic

Non-T2 Asthma

variably associated with:

- Th1 (CD4+IFNy+)
- Th17 (IL17A+IL17F+ cells)
- Serum IL-6
- Obesity

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Characterize Endotype

T2 Biomarkers:

- Exhaled nitric oxide
- Total serum IgE and RAST testing
- Peripheral blood eosinophils
- Sputum differential
- Note that if a pt is on high dose ICS or OCS blood eos ≥150, FeNO ≥ 20, sputum eos ≥ 2%, or allergen-driven asthma can identify T2 immunity.

Other:

- Sedimentation rate/C-reactive protein/ANCA
- Aspergillus precipitating antibody
- Aspirin challenge or urinary LTE_4

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Endotype-Driven Medications

T2

- Omalizumab
- Mepolizumab
- Benralizumab
- Reslizumab
- Dupilumab
- Tezepelumab

Non-T2

- LAMA
- Azithromycin
- Tezepelumab
- Other….

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Assessment of Asthma Risk

Risk factors for fatal asthma:

- Prior intubation or ICU level care
- Multiple ED visits, hospitalizations, steroid courses
- Rapid onset severe airflow obstruction
- Depression / medication inaccessibility

Risk factors for decline in lung function:

- Recurrent exacerbations
- Elevated FENO
- Baseline low FEV1

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High-Risk Patients

- Asthma action plan
- Frequent outreach
- Oral steroids available at home
- Home nebulizer/portable nebulizer
- Epi-pen

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Summary

Evaluation is designed to:

- ensure correct diagnosis
- assess and manage co-morbidities
- optimize medication adherence
- characterize asthma endotype
- ensure safety

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Summary (cont.)

Initial evaluation of severe asthma in most patients is likely to include:

- Spirometry / Full PFTs
- Chest imaging, often including chest CT
- Allergy assessment
- Total IgE, CBC with differential, FENO
- Sputum analysis

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Summary

Additional evaluation guided by the history and physical examination and can be quite broad, depending on the clinical suspicion as to what is making this patient's asthma difficult-to-treat and therefore different than the other 90% of persons with asthma.

The Team

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