Asthma

Asma. S. Albtoosh,MD

Department of respiratory and sleep medicine

JUH

Definition

- Asthma: Asthma is a chronic disease characterized by recurrent attacks of shortness of breath and wheezing.
  - Vary in severity and frequency from person to person.
  - May become worse during physical activity or at night.

Definitions:

The definition of severe asthma requires that one or both of the following levels of treatment for the previous year has been needed to prevent asthma from becoming uncontrolled or asthma that remains uncontrolled despite this level of treatment:

- Treatment with guidelines suggested medications for GINA steps 4-5 asthma (high dose inhaled glucocorticoid* and long-acting beta agonist [LABA] or leukotriene modifier/theophylline) for the previous year
- Treatment with systemic glucocorticoid for ≥50% of the year

Uncontrolled asthma is defined as at least one of the following:

- Poor symptom control: ACQ consistently ≥1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
- Frequent severe exacerbations: two or more bursts of systemic glucocorticoids (three or more days each) in the previous year
- History of serious exacerbation: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year
- Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Factors contributing to the rise of bronchial asthma in the region

- Increasing air pollution
- Fast modernization
- Widespread construction work
- Western diet
- Improved standard of living with reduced exercise rates
- Smoking

Asthma in Jordan

- Asthma is moderately common in Jordan.
- No difference in prevalence of asthma diagnosed by a physician between an urbanized region and Bedouins having low socioeconomic status
- Common in male children (similar to other reports)
- **Twofold increase in the prevalence of asthma in Jordan in the last 10 years**

(*Allergy Asthma Proc 30:181–185, 2009; doi: 10.2500/aap.2009.30.3208*)

Pathophysiology

- Airway inflammation
- Intermittent airflow obstruction
- Bronchial hyperresponsiveness

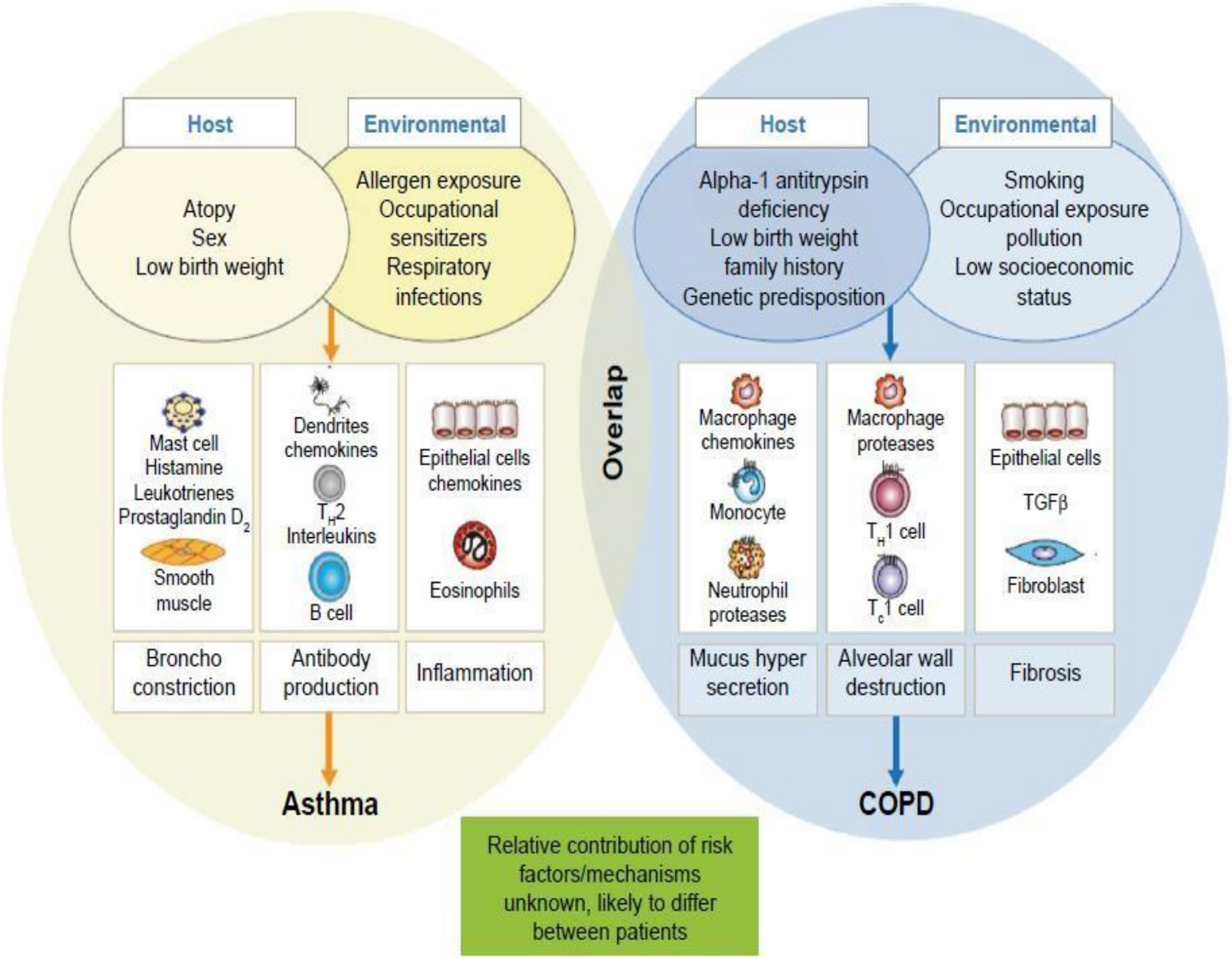
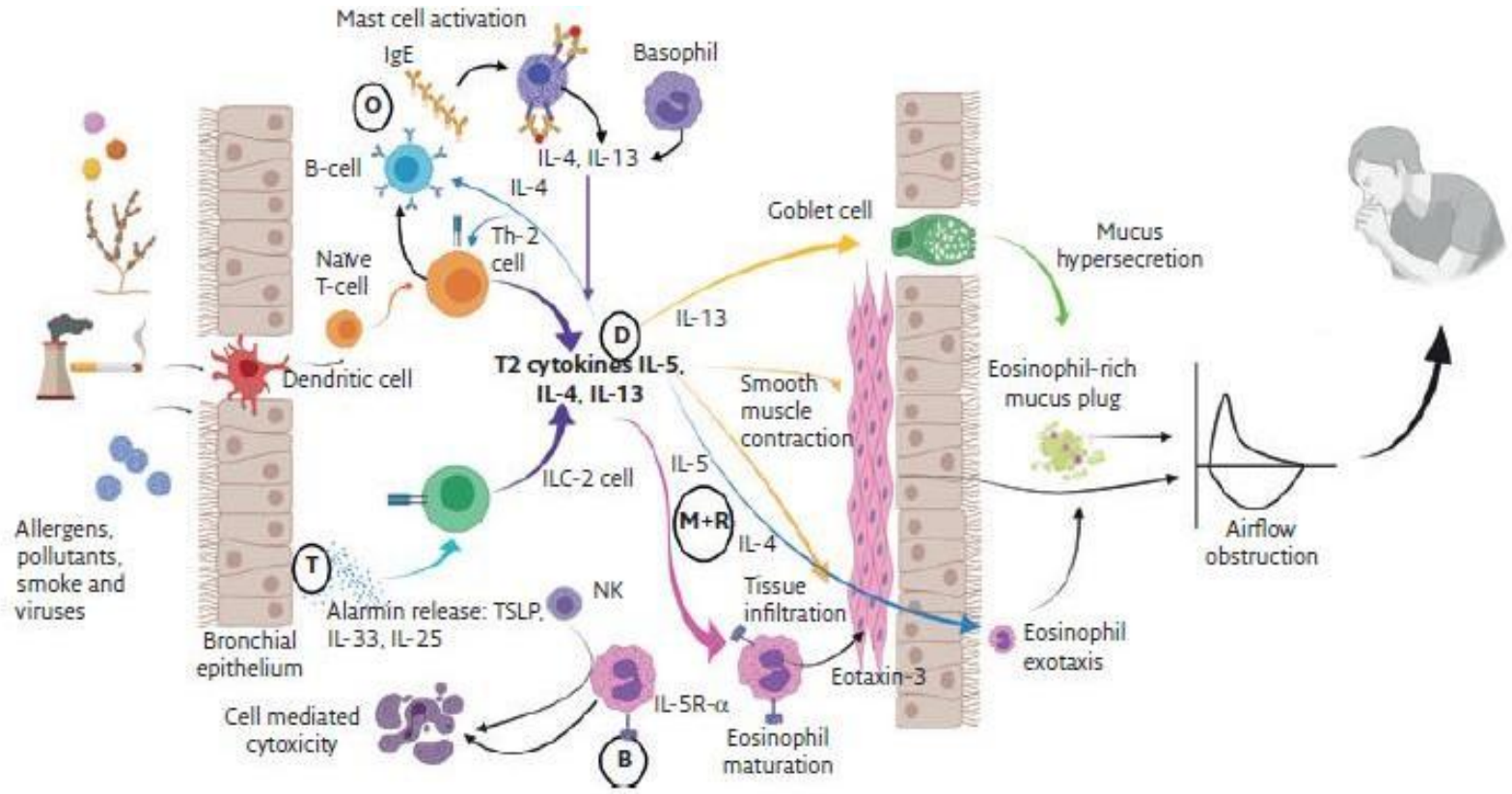
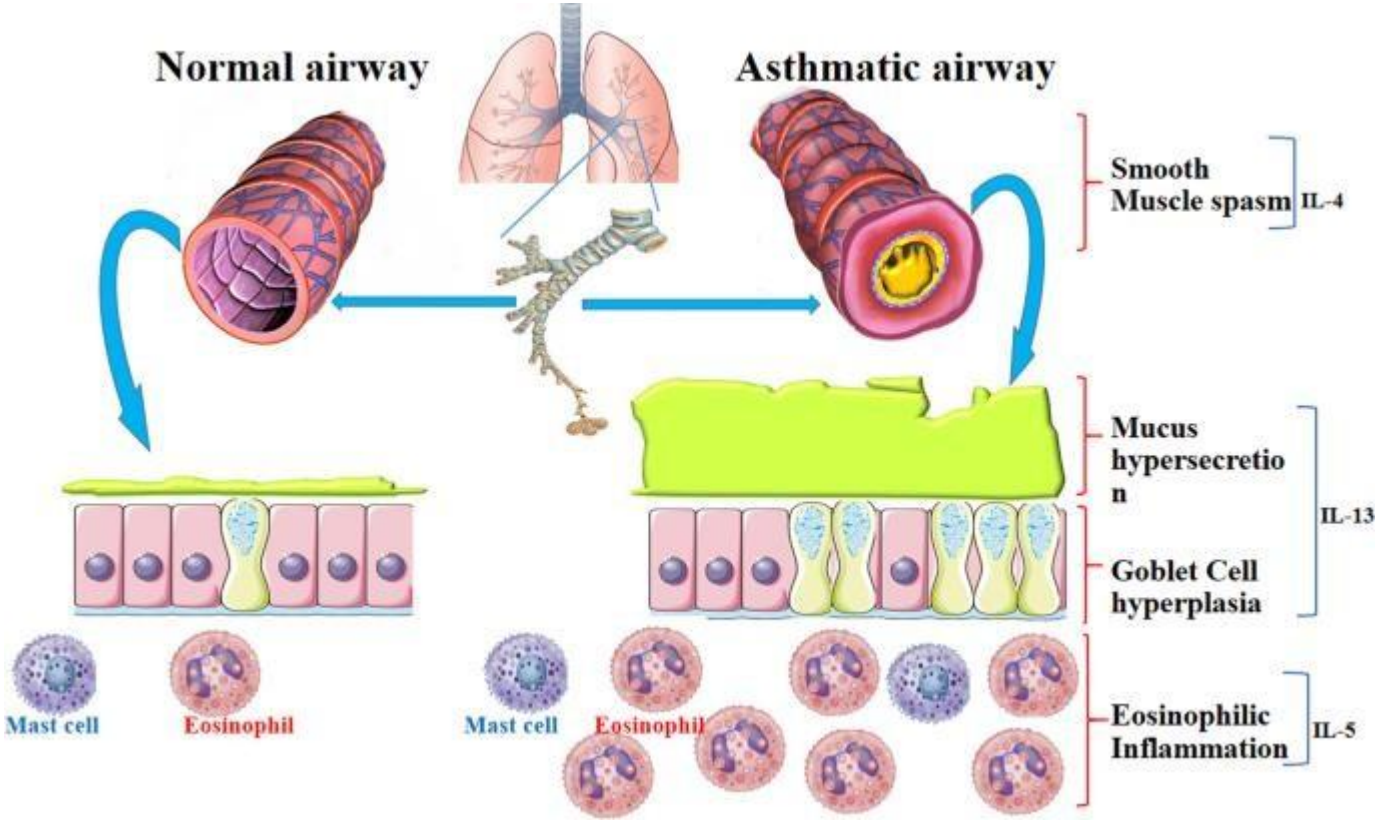


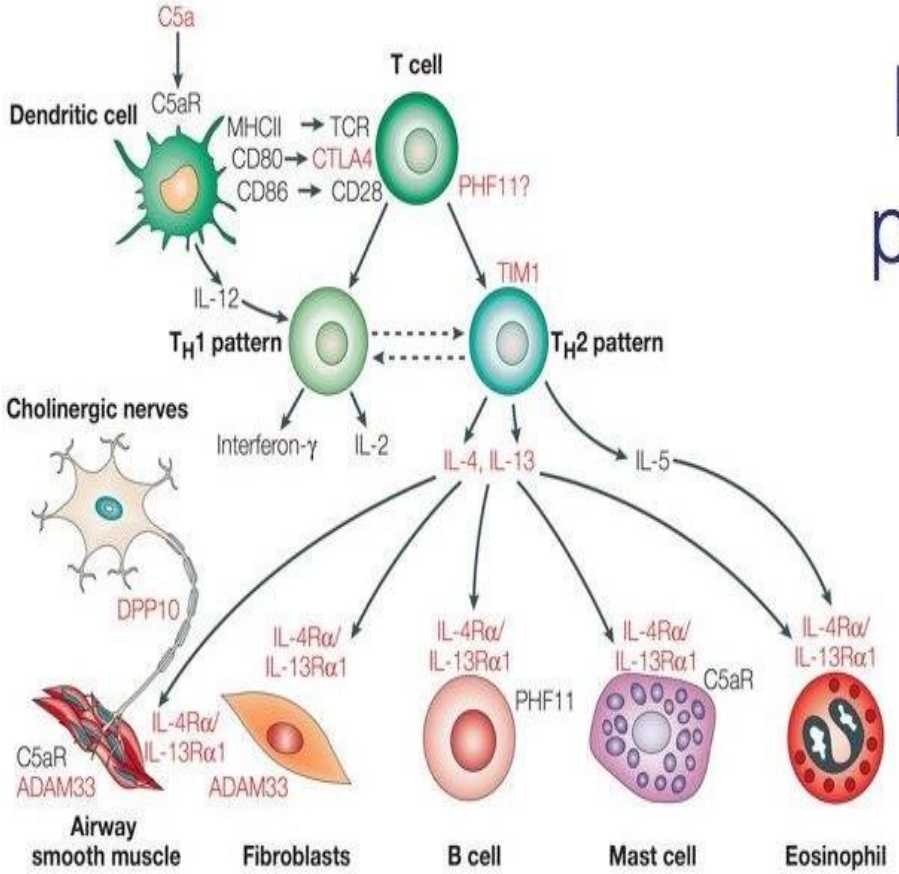
Figure 2 Pathophysiology of asthma, COPD, and overlap.
Notes: Data taken from Postma et al[25] and Barnes et al.[27]
Abbreviations: TGFβ, tumor growth factor β; T_H1, T-helper 1; T_c1, type 1 cytotoxic T cells.

Pathophysiology:




Normal airway
Asthmatic airway
Smooth Muscle spasm
IL-4
Mucus hypersecretion
Goblet Cell hyperplasia
IL-13
Eosinophilic Inflammation
IL-5
Mast cell
Eosinophil
Mast cell
Eosinophil

Pathways in the pathogenesis of asthma



Wills-Karp et al,
Nat Genet 5: 376-387, 2004

Airway Obstruaction (causes)

- Acute bronchoconstriction: IgE-dependent mediator release following exposure to allergens (early asthma response)
- Airway edema: 6-24 hours following allergen challenge (late asthma response).
- Chronic mucous plug formation: exudate of serum proteins and cell debris, may take weeks to resolve
- Airway remodeling: due to structural changes due to long-standing inflammation, affects the extent of reversibility of airway obstruction

Bronchial Hyperresponsiveness

- Hyperinflation compensates for the airflow obstruction leading to hypoventilation, vasoconstriction and ventilation-perfusion mismatch.

4 stages of blood gas progression with status asthmaticus

	$PaCO_2$	PaO_2
Stage 1	Decrease	Normal
Stage 2	Decrease	Decreased
Stage 3	NORMAL	Decreased
Stage 4	High	Decreased

Etiology

- Environmental allergens (eg, house dust mites; animal allergens, especially cat and dog; cockroach allergens; and fungi)
- Viral respiratory tract infections
- Exercise, hyperventilation
- GERD
- Chronic sinusitis or rhinitis
- ASA,NSAID hypersensitivity, sulfite sensitivity
- Perinatal factors (prematurity and increased maternal age; maternal smoking and prenatal exposure to tobacco smoke

Etiology

- Beta-adrenergic receptor blockers (including ophthalmic preparations)
- Obesity
- Environmental pollutants, tobacco smoke
- Occupational exposure
- Irritants (eg, household sprays, paint fumes)
- Various high- and low-molecular-weight compounds (eg, insects, plants, latex, gums, diisocyanates, anhydrides, wood dust, and fluxes; associated with occupational asthma)
- Emotional factors or stress

Aspirin-Induces Asthma

- Asthma, aspirin sensitivity, and nasal polyps
- 5-10% of patients with asthma
- Third to fourth decade
- Can occur with other NSAIDS
- Caused by an increase in eosinophils and cysteinyl leukotrienes after exposure
- Management:
  - Avoidance of these medications
  - Leukotriene antagonists, may allow patients to take daily aspirin for cardiac or rheumatic disease
  - Aspirin desensitization decreases sinus symptoms, allowing daily dosing of aspirin

GERD

- A definite asthma-causing factor (defined by a favorable asthma response to medical antireflux therapy) in 64% of patients; clinically silent reflux was present in 24% of all patients
- Aggressive antireflux therapy may improve asthma symptoms, pulmonary function, or unexplained chronic cough.

Occupational Asthma

- 10-15% of adult asthma cases
- High-risk jobs: farming, painting, janitorial work, and plastics manufacturing
- ACCP consensus statement: work-related asthmas as including occupational asthma (ie, asthma induced by sensitizer or irritant work exposures) and work-exacerbated asthma (ie, preexisting or concurrent asthma worsened by work factors)

Not included

Occupational Asthma

- Types of occupational asthma:
  - Immune-related
    - Has a latency of months to years after exposure
  - Non-immune-related (irritant-induced asthma (reactive airway dysfunction syndrome)
    - Has no latency period and may occur within 24 hours after an accidental exposure to high concentrations of respiratory irritants
- Asthmatics with worsening of symptoms during the week and improvement during the weekends should be evaluated for occupational exposure.

- Peak-flow monitoring during work (optimally, at least 4 times a day) for at least 2 weeks and a similar period away from work is one recommended method to establish the diagnosis. [

Viruses and Asthma

- Rhinovirus illness during infancy: significant risk factor for the development of wheezing in preschool children and a frequent trigger of wheezing illnesses in children with asthma
- 80-85% of childhood asthma episodes are associated with prior viral exposure
- Prior childhood pneumonia due to infection by respiratory syncytial virus, *Mycoplasma pneumoniae,* and/or *Chlamydia* species was found in more than 50% of a small sample of children aged 7-9 years who later had asthma.
- smoke exposure is associated with increased infection with RSV/ childhood asthma

Sinusitis (United Airways)

- Of patients with asthma, 50% have concurrent sinus disease
- Important exacerbating factor for asthma symptoms
- Treatment of nasal and sinus inflammation reduces airway reactivity
- Treatment of acute sinusitis requires at least 10 days of antibiotics to improve asthma symptoms

Exercise-induced asthma

- Exercise triggers acute bronchoconstriction in persons with heightened airway reactivity
- Any age
- Primarily in persons who have asthma
- Also in patients with normal resting spirometry findings with atopy, allergic rhinitis and cystic fibrosis
- In healthy persons: elite or cold weather athletes
- The underlying asthma may be silent in as many as 50% of patients, except during exercise

Exercise-induced asthma

- Pathogenesis:
- Water and/or heat loss from the airway
- BAL: no increase in inflammatory mediators
- Refractory period, during which a second exercise challenge does not cause a significant degree of bronchoconstriction
- Warm up and B2 agonist

Obesity

- Significant association between asthma and abnormal lipid and glucose metabolism.
- High BMI: worse asthma control
- Sustained weight loss improves asthma control
- Accelerated weight gain in early infancy is maybe associated with increased risks of asthma symptoms

Presentation

- History
  - Is this Asthma?
  - Family history: allergy, sinusitis, rhinitis, eczema, and nasal polyps
  - Asthma severity
  - Precipitating factors
  - Social history: smoking, workplace or school characteristics, educational level, employment, social support, compliance with medications, and illicit drug use

Exacerbation History

- Prodromal signs or symptoms
- Rapidity of onset
- Associated illnesses
- Number in the last year
- Need for emergency department visits, hospitalizations, ICU admissions, intubations
- Missed days from work /school or activity limitation

Symptoms

- Wheezing is one of the most common symptoms
- Mild: only end expiratory
- As severity increases: lasts throughout expiration
- Severe asthmatic episode: also present during inspiration
- Most severe: absent because of the severe limitation of airflow associated with airway narrowing and respiratory muscle fatigue.

Asthma and Wheezing

- Asthma can occur without wheezing: obstruction involves predominantly the small airways
- Can be associated with other causes
  - Cystic fibrosis, heart failure
  - Vocal cord dysfunction (inducible laryngeal obstruction (ILO) Predominantly inspiratory wheeze , heard best over the laryngeal area in the neck.
  - Dynamic airway collapse: bronchomalacia, or tracheomalacia: expiratory wheeze heard over the large airways

Cough

- May be the only symptom of asthma, especially in cases of exercise-induced or nocturnal asthma

- Nonproductive and nonparoxysmal

- In nocturnal asthma: after midnight and during the early hours of morning.

Others

- Chest tightness/pain (with or without other symptoms of asthma) especially in exercise-induced or nocturnal asthma.

- Nonspecific symptoms in infants or young children:
  - Recurrent bronchitis, bronchiolitis, or pneumonia; a persistent cough with colds; and/or recurrent croup or chest rattling

Exercise-induced bronchoconstriction

- Only with exercise
- Cough, wheezing, shortness of breath, and chest pain or tightness
- Sore throat or GI upset
- 10 minutes into the exercise
- Short exercise period: symptoms may develop up to 5-10 minutes after completion of exercise
- Higher intensity, more intense attack

Physical Examination

- Mild episodes
  - Shortness of breath with physical activity
  - Can talk in sentences and lie down
  - May be agitated
  - Respiratory rate is increased
  - No use of accessory muscles
  - Heart rate is less than 100 bpm
  - Moderate expiratory wheezing
  - O2 saturation is greater than 95%

Physical Examination

- Moderately severe episodes:
  - Use of accessory muscles
  - In children: supraclavicular and intercostal retractions, nasal flaring, abdominal breathing
  - The heart rate is 100-120 bpm
  - Loud wheezing
  - **Pulsus paradoxus**: (fall in systolic blood pressure during inspiration of10-20 mm Hg)
  - O2 sat is 91-95%
  - Sitting position

Physical Examination

Severe episode

- Shortness of breath at rest
- Talk in words
- Respiratory rate: greater than 30/min
- Use of accessory muscles
- Heart rate is more than 120 bpm
- Loud biphasic (expiratory and inspiratory) wheezing
- Pulsus paradoxus is often present (20-40 mm Hg)
- O2 sat less than 91%
- Sitting position: tripod position.

Impending Respiratory Failure

- Drowsy and confused
- Thoracoabdominal movement
- Wheezing may be absent
- Severe hypoxemia, bradycardia
- Pulsus paradoxus may be absent: suggests respiratory muscle fatigue.
- Diaphoresis
- Rise in PCO_2 and hypoventilation
- Life-threatening hypoxia, advanced hypercarbia, bradypnea, somnolence

Nonpulmonary Manifestations

- Signs of atopy or allergic rhinitis, such as conjunctival congestion and inflammation, ocular shiners, a transverse crease on the nose due to constant rubbing
- Pale nasal mucosa
- Erythematous Turbinates
- Nasal polyps
- Atopic dermatitis
- Eczema

Asthma Classification

- The severity of asthma is classified as the following:
  - Intermittent
  - Mild persistent
  - Moderate persistent
  - Severe persistent

- Patients with asthma of any level of severity may have mild, moderate, or severe exacerbations

- The presence of one severe feature is sufficient to diagnose severe persistent asthma

Asthma Differential Diagnoses

- Vocal cord dysfunction or inducible laryngeal obstruction (ILO): paradoxical adduction of the vocal cords during inspiration, and may disappear with panting, speech, or laughing
  - Direct laryngoscopy during symptomatic periods or after exercise
  - The presence of flattening of the inspiratory limb of the flow-volume loop may also suggest vocal cord dysfunction, but this is only seen in 28% of patients at baseline]
- Tracheal and bronchial lesions
- Foreign bodies

Asthma Differential Diagnoses

- Congestive heart failure (cardiac asthma)
  - Engorged pulmonary vessels and interstitial pulmonary edema, which reduce lung compliance and contribute to the sensation of dyspnea and wheezing
  - Wheezing secondary to bronchospasm: related to paroxysmal nocturnal dyspnea and nocturnal coughing

Asthma Differential Diagnoses

- Sinus disease
- Gastroesophageal reflux

Asthma Workup

not routinely done, only used to confirm the diagnosis.

- Blood and sputum eosinophilia:
  - Greater than 4% (blood) supports the diagnosis of asthma
  - Its absence does not exclude asthma
  - Greater than 8% may be observed in patients with:
    - ❖ Atopic dermatitis. With skin rash
    - ❖ Allergic bronchopulmonary aspergillosis. IgE is more than 1000, high eosinophils and parenchymal changes
    - ❖ EGPA, interstitial lung disease (fibrosis)
    - ❖ Eosinophilic pneumonia, with reversed pulmonary edema
  - Use mepolizumab (anti-IL-5 antibody) if counts 150 cells/µL or an eosinophil count of 300 cells/µL within the past 12 months
  - Adjust ICS with sputum eosinophilia

Asthma Workup

- Serum Immunoglobulin E:
  - Total serum immunoglobulin E levels greater than 100 IU are frequently observed in patients experiencing allergic reactions
  - Observed also in: (allergic bronchopulmonary aspergillosis, EGPA)
  - Normal levels do not exclude the diagnosis of asthma
  - Elevated levels are required for chronic asthma patients to be treated with omalizumab (Xolair)

Chest Radiography

- Reveals complications
- Alternative causes of wheezing
- Normal or hyperinflation
- Exclude pneumothorax or pneumomediastinum

Chest CT Scanning

Not included

- Bronchial wall thickening
- Bronchial dilatation
- Cylindrical and varicose bronchiectasis
- Reduced airway luminal area
- Mucoid impaction of the bronchi
- Centrilobular opacities, or bronchiolar impaction
- Linear opacities
- Airtrapping, as demonstrated or exacerbated with expiration mosaic lung attenuation, or focal and regional areas of decreased perfusions

Pulmonary Function Testing

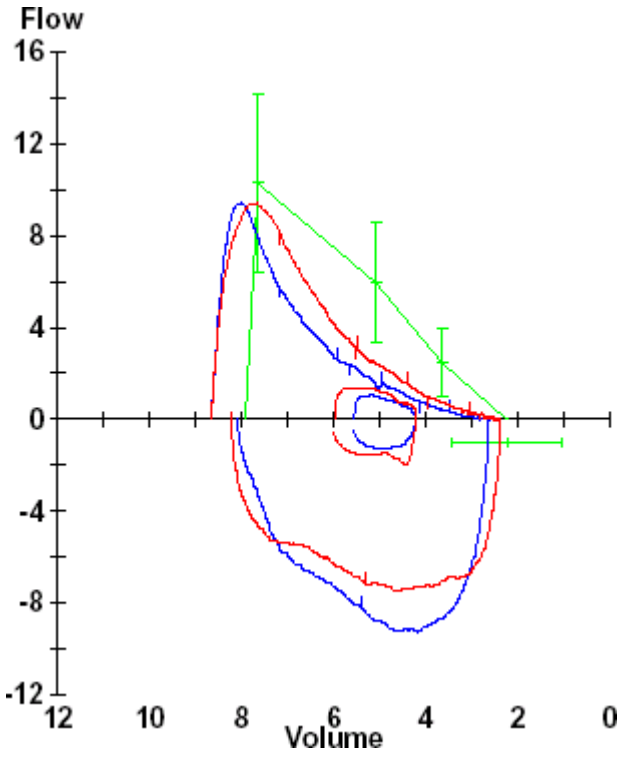
- Establish asthma diagnosis
- Prior to initiating treatment
- Should include measurements before and after inhalation of a short-acting bronchodilator
- Reduced FEV_1/FVC (airway obstruction)
- Reversibility: increase of 12% and 200 mL after the administration of a short-acting bronchodilator

to confirm the diagnosis of asthma, we use forced spirometry with FEV1/FVC less than 70% or below the lower limit of normal, with reversibility.

Bronchodilator Response PFT

ID: AKC1991 Date: 21/06/04 Gender: Male Age: 40
Weight(kg): 96.0 Height(cm): 189 BMI: 26.87
PB: 745 Temp: 21

Spirometry	Pre Ref	Pre Meas	Post % Ref	Post Meas	Post % Ref	% Chg
FVC	5.71	6.05	106	6.31	110	4
FEV_1	4.27	3.74	88	4.27	100	14
FEV_1/FVC	74.0	62.0		68		
FEF_{25-75}%	4.19	(1.99)	(47)	2.66	63	33
PEF	10.27	10.19	99	9.4	91	-8
Lung Volumes						
TLC						
RV						
RV/TLC						
FRC PL						
ERV						
VC						
Resistance						
Raw						
sRaw						
Diffusion						
D_{LCO}						
D_{LCO} /V_A						
V_A						



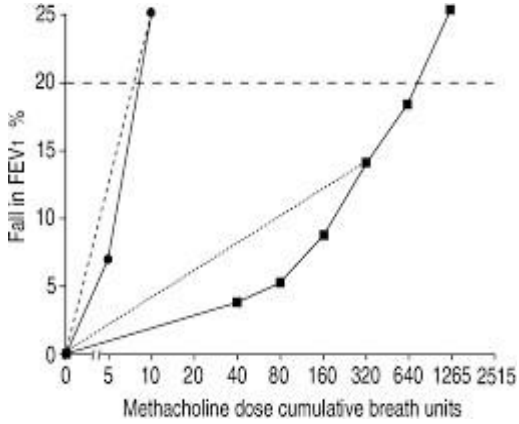
Bronchodilator (BD) responsiveness

- **Untreated asthma:** patients obtain quick symptomatic relief with rapid-onset BD
  - Reflected in an increase in FEV_1 and PEF (and sometimes FVC) within 10-15 minutes
- **Random BD testing** has very limited utility, especially if long after disease onset *(Beasley et al, AJRCCM 2024)*
  - Asthma is variable: symptoms (and bronchoconstriction) not present all the time
  - ICS-containing treatment → increased pre-bronchodilator FEV_1 → decreased BD responsiveness
  - Longer asthma duration → some patients develop persistent airflow limitation → decreased BD responsiveness
  - Some patients with a diagnosis of COPD (with/without asthma) have significant BD responsiveness
- **Current ERS/ATS criterion for BD responsiveness in clinical practice** is an increase in FEV_1 or FVC from baseline by ≥12% and ≥200 mL of the **baseline** value
  - Used as one of gold standards in 2022 ERS Guidelines on Diagnosis of Asthma *(Louis et al, ERJ 2022)*
- **ERS/ATS Technical Standards Committee** proposed changing this criterion to an increase in FEV_1 or FVC from baseline by >10% of the **predicted** value *(Stanojevic et al, ERJ 2021)*
  - Based on data for mortality; not compared with other diagnostic tests for asthma
  - The Technical Committee did not advocate adoption of this change for clinical practice
- GINA will review this again when more data are available; no change recommended in the meantime

Methacholine/histamine challenge

- When spirometry is normal or near normal
- In patients with intermittent or exercise-induced asthma symptoms
- Testing helps determine if airway hyperreactivity is present
- A negative test result excludes the diagnosis of asthma
- Methacholine: a direct stimulant that acts directly on acetylcholine receptors on smooth muscle, causing contraction and airway narrowing

Methacholine/histamine challenge



- Methacholine is administered in incremental doses up to a maximum dose of 16 mg/mL.
- 20% decrease in FEV_1, up to the 4 mg/mL level, is considered a positive test result.
- The presence of airflow obstruction with an FEV_1 less than 65-70% at baseline is generally an indication to avoid performing the test.

Or a 15% decrease in mannitol test

Exercise testing

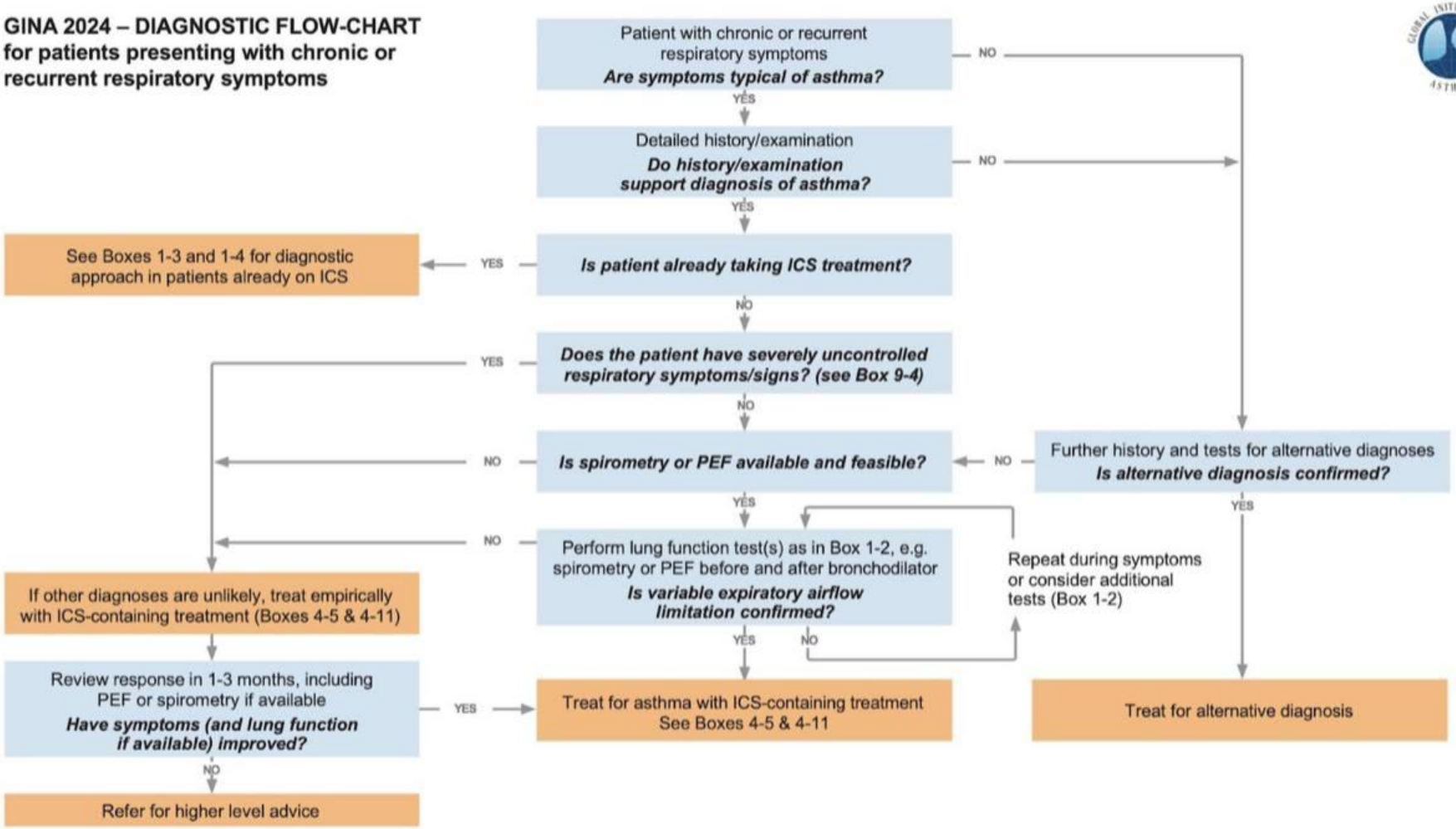
Not included

- 6-10 minutes of strenuous exertion at 85-90% of predicted maximal heart rate and measurement of postexercise spirometry for 15-30 minutes
- A positive test: a 15% decrease in FEV_1 after exercise.

Peak Flow Monitoring

- Common in the ED
- Serial measurements document response to therapy
- Variablity of 20% between morning and night .
- Helpful in determining whether to admit the patient to the hospital or discharge from the ED (if more than 70% 60 min post last treatment)
- A limitation of PEF is that it is dependent on effort by the patient.

GINA 2024 – DIAGNOSTIC FLOW-CHART for patients presenting with chronic or recurrent respiratory symptoms



Asthma is often inappropriately treated as a recurrent acute disease, with no treatment in between

- Burden to patients, family, health system, economy
- Risk of asthma mortality
- Cumulative risk of adverse effects of oral corticosteroids, with even 4–5 lifetime courses *(Price, 2018)*
- Asthma morbidity and mortality are largely preventable

GINA goal of asthma management

The goal is to achieve the **best possible long-term asthma outcomes** for each patient:

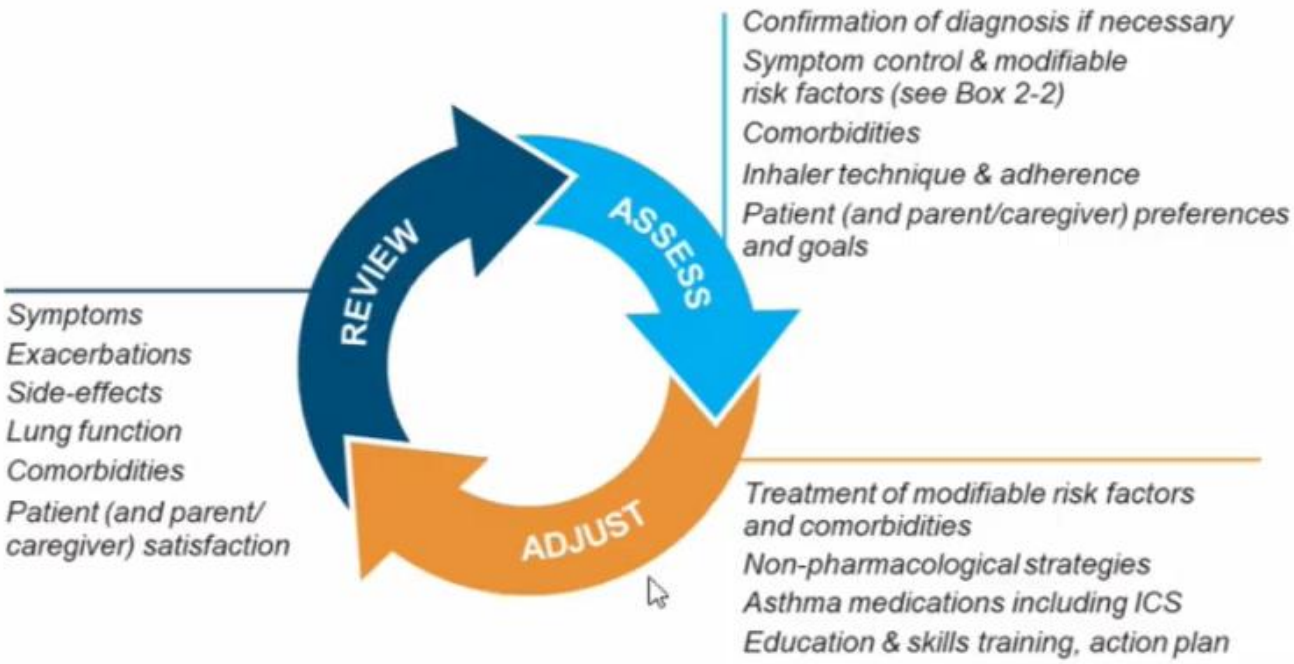
- Long-term symptom control, which may include:
  - Few/no asthma symptoms, quickly relieved
  - No sleep disturbance
  - Unimpaired physical activity
- Long-term asthma risk minimization, which may include:
  - No exacerbations
  - Improved or stable personal best lung function
  - No requirement for maintenance oral corticosteroids
  - No medication side-effects

When discussing best possible long-term outcomes with a patient, consider:

- Their asthma phenotype
- Clinical features
- Multimorbidity
- Risk factors (e.g. poor adherence, smoking, persistent airflow limitation)
- Availability, cost and adverse effects of medications
- The patient's goals (these may be different from medical goals)

- Assessing symptom control is not enough! Patients with few asthma symptoms can still have severe or fatal exacerbations related to individual risk factors or external triggers (viruses, allergen, pollution)
- Encourage referral for expert advice for patients with difficult-to-treat or severe asthma

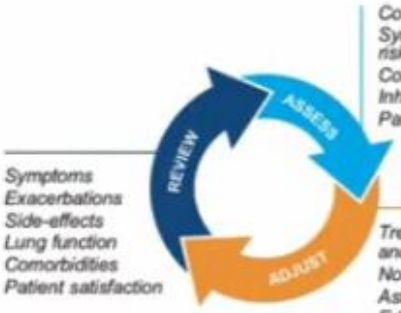
Asthma treatment is not 'set and forget', and not just medications



GINA 2024 Box 3-3

GINA 2024 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS (as below)
Education & skills training

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

See GINA severe asthma guide

TRACK 2: Alternative **CONTROLLER and RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

Other controller options (limited indications, or less evidence for efficacy or safety – see text)

Low dose ICS whenever SABA taken, or daily LTRA†, or add HDM SLIT*	*Medium dose ICS, or add LTRA†, or add HDM SLIT*	*Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only*	*Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects*	

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

GINA 2024 Box 4-6

Biologics classes

Class	Name	Age*	Asthma indication*	Other indications*
Anti-IgE	Omalizumab (SC)	≥6 years	Severe allergic asthma	Nasal polyposis, chronic spontaneous urticaria
Anti-IL5 Anti-IL5R	Mepolizumab (SC) Reslizumab (IV) Benralizumab (SC)	≥6 years ≥18 years ≥12 years	Severe eosinophilic/Type 2 asthma	Mepolizumab: EGPA, CRSwNP, hypereosinophilic syndrome
Anti-IL4R	Dupilumab (SC)	≥6 years	Severe eosinophilic/Type 2 asthma, or maintenance OCS	Moderate-severe atopic dermatitis, CRSwNP
Anti-TSLP	Tezepelumab (SC)	≥12 years	Severe asthma	

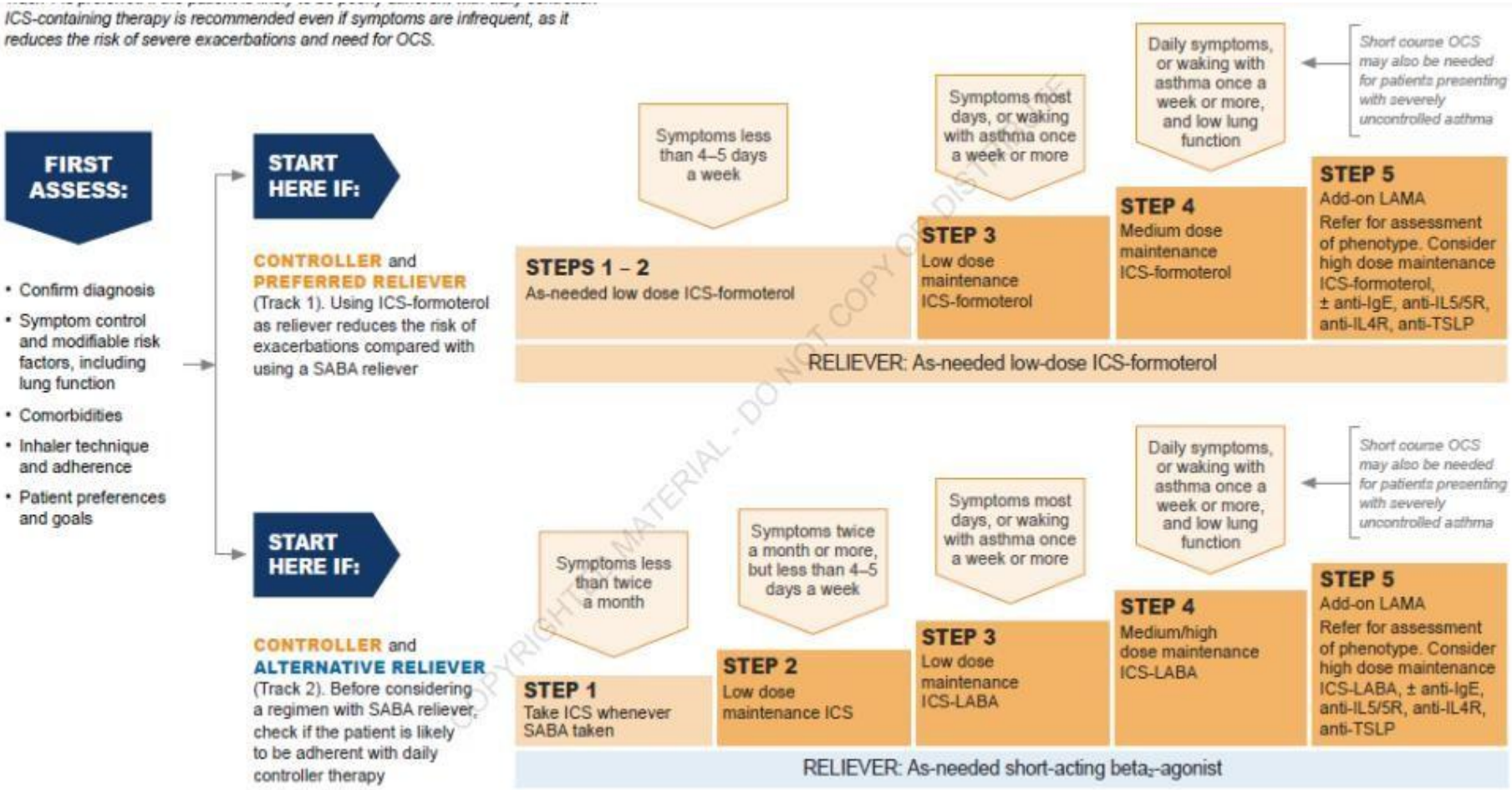
Asthma Treatment & Management

Goals for treating asthma

- Avoid troublesome symptoms night and day
- Use little or no reliever medication
- Have productive, physically active lives
- Have (near) normal lung function
- Avoid serious attacks(Exacerbations)

- A stepwise (step-up/step-down) approach
- For all patients: quick-relief medications include rapid-acting beta$_2$ agonists as needed for symptoms
- Intensity depends on the severity of symptoms
- If rapid-acting beta$_2$ agonists are used more than 2 days a week for symptom relief (not including use of rapid-acting beta$_2$ agonists for prevention of exercise-induced symptoms), stepping up on treatment may need be considered

GINA 2022 guidelines:



Environmental control

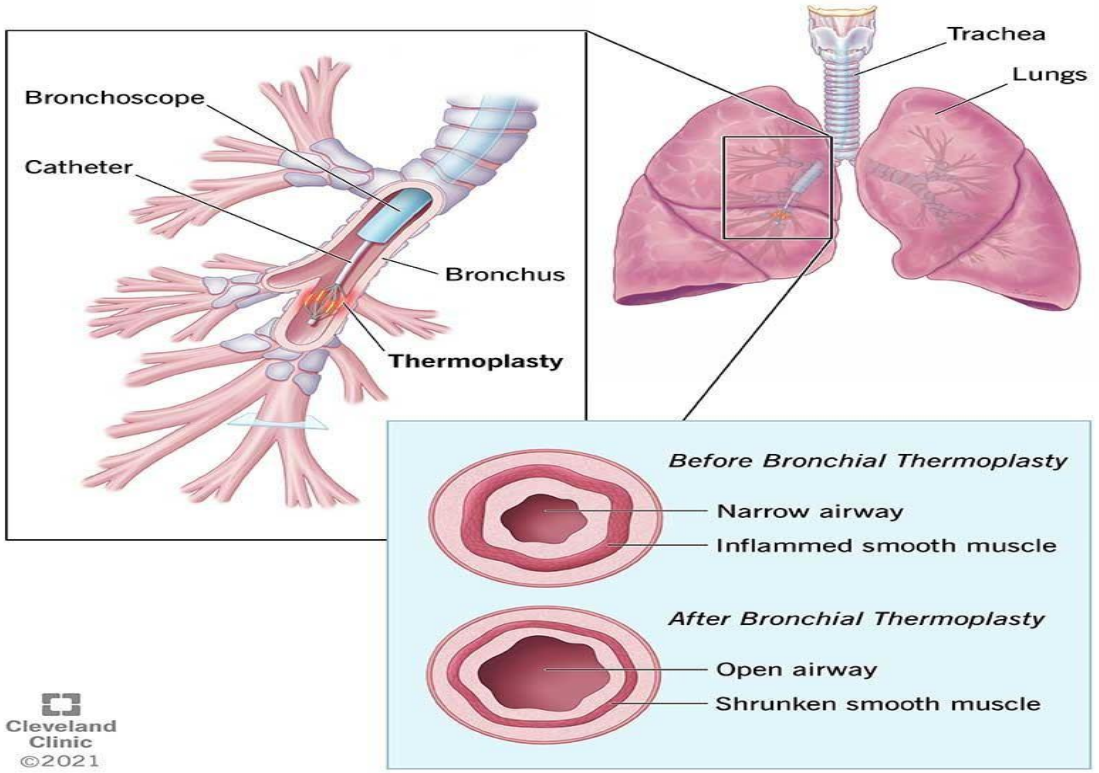
- Avoid smoking
- Control dust mites
- Pets: effect may last up to 6 months after pet removal
- Cockroaches
- Mold
- Pollen

Monoclonal Antibody Therapy

- Omalizumab:
  - IgG antibody against IgE
  - Given by subcutaneous injection every 2-4 weeks
  - moderate-to-severe persistent asthma
  - Positive skin test result or in vitro reactivity to a perennial aeroallergen
  - Symptoms are inadequately controlled with inhaled corticosteroids
  - IgE levels between 30 and 700 IU
  - Should not weigh more than 150 kg

Bronchial Thermoplasty

- controlled thermal energy is delivered to the airway wall during a series of bronchoscopy procedures



Acute Exacerbation

- Short acting bronchodilators .
- Steroids
- Heliox: 80:20
- Intubation

Asthma in Pregnancy

- Complicates 4-8% of pregnancies
- Severe and poorly controlled :

  prematurity,

  low birth weight

  perinatal mortality
- Maintain adequate oxygenation of the fetus by prevention of hypoxic episodes in the mother

THANK YOU!

Thanks for **Mira** for Putting the new info in slides 😊