ASTHMA
CLASSIFICATION, DIFFRENTIAL DIAGNOSIS & COMORBIDITIES

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- Asthma is a heterogeneous disease, with different underlying disease processes. Recognizable clusters of Demographic, Clinical and/or pathophysiological characteristics are often called “ASTHMA Phenotypes”.
- In patients with more severe asthma, some phenotype-guided treatments are available.
- However, no strong relationship has been found between specific pathological features and particular clinical patterns or treatment responses.
- Many clinical phenotypes of Asthma have been identified.
- Some of the most common are:

Endo type	Phenotype	Clinical characteristics	Molecular mechanism	Biomarkers	Natural history
TH2 high	Atopic	Well defined, early onset, steroid sensitive	Allergic sensitization	Blood/sputum eosinophil count, serum specific allergen Ig E, high FeNO, high total Ig E	Identifiable and treatable, preserved lung function
	Late onset	± concomitant CRSwNP, steroid refractory	*Staphylococcus aureus* enterotoxin	Blood/sputum eosinophil count, high FeNO	Severe from onset, more frequent exacerbation
	AERD	Adult onset	Dysregulated arachidonic acid metabolism	Blood/sputum eosinophil count, urinary LTE4	Severe from onset, more frequent exacerbation
Non-TH2	Non-atopic	Adult onset—paucigranulocytic or neutrophilic	NLRP3/1L-1 β, altered micro-RNA expression, Thl7	Induced sputum neutrophil count, MMP-9 in BAL	Variable course and lung function
	Smokers	Older adults	Oxidative stress, mixed Th2 high/Th2 low	Induced sputum neutrophil count	More frequent exacerbation, lower lung function
	Obesity related	Female sex	Oxidative stress, neutrophils, increased innate immune activation	Serum IL-6	Severe symptoms, preserved lung function
	Elderly	> 50 to > 65 years at onset	Immunosenescence, Thl/Thl7 inflammation	Induced sputum neutrophil count	Steroid resistant

ALLERGIC ASTHMA

- The most easily recognized Asthma phenotype, which often commences in childhood and is associated with Past/Family Hx of Allergic disease such as eczema, allergic rhinitis or food or drug allergy. Examination of induced-sputum of these patients before treatment often reveals eosinophilic airway inflammation.
- Patients usually respond well to inhaled corticosteroid (ICS) treatment.

ADULT-ONSET(LATE-ONSET) ASTHMA

- Some adults, particularly women, present with Asthma for the first time in adult life. They tend to be non-allergic. A subset of T2-high phenotype of unknown molecular mechanism. Airway T2 inflammation is not ameliorated by ICS therapy in approximately half of asthmatics, and these patients are older and have more severe asthma with fixed airflow obstruction. The great majority of these patients have comorbid chronic rhinosinusitis with nasal polyps (CRSwNP) which generally precedes asthma development.

- This phenotype is generally characterized by prominent blood and sputum eosinophilia refractory to inhaled/oral corticosteroid treatment. There is generally no evidence of atopy. A recent cluster analysis identified an endo type of asthma with CRSwNP that highly expresses *Staphylococcus aureus* enterotoxin (SE) specific Ig E and high levels of IL-5 and Ig E . Some of these patients have sputum neutrophilia in addition to eosinophilia, implicating Th2/Th17 interactions . These patients generally have also high FeNO and normal or elevated serum total Ig E. The recognition of this phenotype may be an indication to escalate therapy earlier. Occupational asthma should be ruled out in patients presenting with adult-onset asthma.

ASTHMA WITH PERSISTANT AIRFLOW LIMITATION

- Some patients with long-standing asthma develop airflow limitation that is persistent or incompletely reversible.
- This is thought to be due to airway remodelling.

ASPIRIN-EXACERBATED RESPIRATORY DISEASE

- It starts with nasal congestion and anosmia, and progresses to chronic rhino sinusitis with nasal polyps that regrow rapidly after surgery. Asthma and hypersensitivity to Aspirin and NSAIDs develop subsequently. Following ingestion of Aspirin or NSAID, an acute Asthma attack develops within minutes to 1-2 hours. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck, and may sometimes progress to severe bronchospasm, shock, LOC and respiratory arrest. AERD is more likely to be associated with low lung function and severe Asthma, and increased need for emergency care.
- Aspirin challenge is gold standard for diagnosis.

- **Aspirin desensitization** — Nearly all AERD patients can be successfully desensitized to aspirin.
- The indications for aspirin desensitization in AERD include the following:
- Nasal polyposis that is worsening or recurring after surgery despite LTMAs, nasal glucocorticoids, and other appropriate therapies

Comorbid inflammatory conditions requiring daily NSAID therapy (eg, arthritis)

- Atherosclerotic heart/vascular disease requiring the anti platelet effects of aspirin
- Recurrent headaches or other conditions requiring intermittent use of NSAIDs after failure of other options

NON-ALLERGIC ASTHMA

- The cellular profile of sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (pauci granulocytic)
- Patients with non-allergic asthma often demonstrate less short-term response to ICS.

Smoking Associated

- The mechanisms underlying smoking-associated asthma is unclear, but it has been considered a T2-low neutrophilic, steroid-resistant phenotype. However, smoking also increases the risk of sensitization to allergens and increases total Ig E demonstrating the link between asthma and COPD. The recently described term "asthma-COPD overlap syndrome (ACOS)" demarcates those patients with a significant smoking history and consequent airflow obstruction but also have overlapping features of asthma (bronchodilator reversibility, eosinophilia, atopy). The current joint task force of the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) published a consensus document outlining diagnostic criteria for ACOS . The committee recommends the presence of all three of the following major criteria and at least one minor criterion for diagnosis. The major criteria include persistent airflow limitation in individuals > 40 years of age with at least 10 pack-years of tobacco smoking, and onset of asthma at < 40 years of age. The minor criteria include a history of atopy, significant bronchodilator reversibility, and peripheral eosinophilia.

ASTHMA WITH OBESITY

- Obesity is an important risk factor for asthma morbidity. The prototypical patient with obesity-associated asthma is the non-atopic, middle-aged woman with severe symptoms despite a moderately preserved lung function. Non-eosinophilic inflammatory mechanisms at the molecular level has been proposed. Another important cytokine, IL-6, has also been recently shown to cause systemic inflammation in a subgroup of asthma patients with obesity and severe disease . The notable observation in this study was increased plasma IL-6 levels in the subset of obese patients with more severe asthma and not in all obese asthmatics. Consequently, both IL-17, IL-22, and IL-6 rather than the T2 cytokines may be clinically relevant in obese patients with severe asthma.

Very Late Onset ELDERLY ASTHMA

- The age cutoff for the diagnosis of very late-onset asthma is not consistent but defined as > 50 years in some studies and > 65 years in others. The aging lung is associated with decreased lung function due to loss of elastic recoil and mechanical disadvantages. In addition to these consequences of normal aging, immunosenescence likely has important consequences in elderly asthmatics . While mechanisms have not been fully elucidated, emerging data suggest that older asthmatics have increased sputum neutrophilia secondary to Th1 and Th17 inflammation

CLASSIFICATION OF ASTHMA

- Assessment of current impairment (based on patient reported Symptoms and measurement of Lung function) and risk of future exacerbations (based on the number of serious exacerbations within the past year)
- - Reported Daytime and Nighttime symptoms, and exercise limitation over the previous two to four weeks.
- -Current values of PEF(peak expiratory flow) and FEV1 and FEV1/FVC
- - Number of exacerbations requiring oral glucocorticoids in the previous year

National Asthma Education and Prevention Program (NAEPP 2020)	*Global Initiative for Asthma (GINA 2021)*
Asthma symptoms/ Lung function	*Asthma symptoms*
Intermittent Asthma/ STEP 1	**STEP 1**
Daytime symptoms<= 2 days/week Nocturnal awakenings<= 2/month Normal FEV1 Exacerbations<= 1/year	Infrequent Asthma symptoms < 2 times/ week

National Asthma Education and Prevention Program (NAEPP 2020)	*Global Initiative for Asthma (GINA 2021)*
Asthma symptoms/ Lung function	*Asthma symptoms*
Mild persistent Asthma/ STEP 2	**STEP 2**
Daytime symptoms >2 but <7 days/week Nocturnal awakenings 3-4 /month Minor interference with activities Normal FEV1 Exacerbations >= 2/year	Asthma symptoms or Need for reliever inhaler >= 2 times/week

National Asthma Education and Prevention Program (NAEPP 2020)	*Global Initiative for Asthma (GINA 2021)*
Asthma symptoms/ Lung function	*Asthma symptoms*
Moderate persistent Asthma/ STEP 3	**STEP 3**
Daytime symptoms Nocturnal awakenings > 1/ week Daily need for SABA Some Activity limitation 60% < FEV1 < 80% Exacerbations >= 2/year	Troublesome Asthma symptoms Most Days Nocturnal awakening due to Asthma >= 1 time/month Risk factors for exacerbations

National Asthma Education and Prevention Program (NAEPP 2020)	*Global Initiative for Asthma (GINA 2021)*
Asthma symptoms/ Lung function	*Asthma symptoms*
Severe persistent Asthma/ STEP 4-6	**STEP 4-5**
Symptoms all day Nocturnal awakenings nightly Need for SABA several times/ day Extreme Activity limitation FEV1 < 60% Exacerbations >= 2/year	Severely uncontrolled Asthma with>=3 of the following: Daytime symptoms >2 times/week Nocturnal awakening due to Asthma Reliever needed >2 times/week Activity limitation OR An Acute exacerbations

DIFFERENTIAL DIAGNOSIS

AGE	SYMPTOMS	CONDITION
12-39 YEARS	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Sudden onset of symptoms, unilateral wheeze	Inhaled foreign body
	Recurrent infections, productive cough	Bronchiectasis
	Cardiac murmurs	Congenital heart dis.
	Dizziness, paresthesia, sighing	Hyperventilation, Dysfunctional breathing
	Dyspnea, stridor	Laryngeal obstruction
	Shortness of breath, F.Hx	Alpha1-anti trypsin deficiency
	Excessive cough, mucus production, GI symptoms	Cystic Fibrosis

AGE	SYMPTOMS	CONDITION
+40 YEARS	Dyspnea, stridor	Laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, Dysfunctional breathing
	Recurrent infections, productive cough	Bronchiectasis
	Cough, sputum, dyspnea on exertion, smoking or noxious exposure	COPD
	Dyspnea on exertion, Nocturnal symptoms, ankle edema	CHF

AGE	SYMPTOMS	CONDITION
+40 YEARS	Treatment with ACE- inhibitor	Medication related cough
	Dyspnea with exertion, non-productive cough, clubbing	Parenchymal Lung disease
	Sudden onset of dyspnea, Chest pain	Pulmonary Embolism
	Dyspnea, unresponsive to bronchodilator	Central Airway obstruction

AGE	SYMPTOM	CONDITION
All AGES	Chronic cough, hemoptysis, dyspnea, fatigue, fever, night sweats, anorexia, weight loss	**Tuberculosis**

COMPLICATING MEDICAL COMORBIDITIES

- - Obesity
- -Gastroesophageal Reflux (GERD)
- - Anxiety and Depression
- - Rhinitis, Sinusitis and Nasal Polyps

ASTHMA IN SPECIFIC POPULATIONS OR SETTINGS

EXERCISE-INDUCED BRONCHOCONSTRICTION **(EIB)**

- Exercise-induced asthma/exercise-induced bronchoconstriction (EIB) is the transient airway narrowing associated with exercise, which can occur in patients with and without chronic asthma.
- The following factors influence the propensity to develop EIB: ambient conditions, type of exercise, and baseline level of airway hyper responsiveness.
- EIB is due to effects of airway cooling/rewarming, dehydration, hyperosmolarity , and mediator release (histamine, leukotrienes, and prostaglandins).
- EIA/EIB occurs in children and adults of all ages at all levels of athletic prowess, from participants in recreational sports to elite athletes.

- While the pathophysiology of EIA/EIB remains the topic of much debate, it likely occurs as a result of changes in airway temperature and osmolarity.
- symptoms usually occur within 5 to 10 minutes following exercise and usually resolve within 30 to 60 minutes following the completion of exercise, with or without the use of bronchodilator medications for rescue.
- EIA/EIB is common among patients with underlying asthma, and exercise is the second-leading trigger for asthma symptoms next to viral upper respiratory infections.
- Regular controller treatment with ICS significantly reduces EIB. Training and sufficient warm-up reduce the incidence and severity of EIB. Taking SABAs, LABAs or chromones prior to exercise prevents EIB, but tolerance to the protective effects of SABAs and LABAs against EIB develops with regular (more than once daily)use.

WOMEN PERIMENSTRUAL (CATAMENIAL)ASTHMA

- In approximately 20% of women ,asthma is worsen in the premenstrual phase. These women tend to be older , have more severe asthma, a higher BMI, a longer duration of asthma, and a greater likelihood of aspirin exacerbated respiratory disease. They more often have dysmenorrhea , premenstrual syndrome, shorter menstrual cycles, and longer menstrual bleeding. The role of hormone levels and systemic inflammation remains unclear.

- -In addition to the usual strategies for management of Asthma, oral contraceptives and/or leukotriene receptor antagonists may be helpful (Evidence D)

OCCUPATIONAL ASTHMA

- In the occupational setting, rhinitis often precedes the development of asthma. Once a patient has become sensitized to an occupational allergen, the level of exposure necessary to induce symptoms may be extremely low; resulting exacerbations become increasingly severe, and with continued exposure ,persistent symptoms and irreversible airflow limitation may result.
- All patients with Adult-onset Asthma should be asked about their work history and other exposures. (Evidence A)
- The early identification and elimination of occupational sensitizers and the removal of patients from any further exposure are important aspects of the management of occupational Asthma.(Evidence A)

ALLERGIC BRONCHO PULMONARY ASPERGILLOSIS (ABPA)

- Repeated episodes of wheezing, fleeting pulmonary opacities, and development of brochiectasis , sometimes with malaise , weight loss and hemoptysis are seen. Some patients expectorate brownish sputum plugs. ABPA is most commonly found in Asthma or cystic fibrosis, due to a hypersensitivity to Aspergillus Fumigatus, a common indoor and outdoor mold.
- Diagnosis is based on composite criteria including immediate hypersensitivity reaction to A.fumigatus, total serum ig E, specific ig G to A.fumigatus, radiologic features and blood eosinophils.

THANKS FOR YOUR ATTENTION