Chronic Obstructive Lung Disease

Amita Vasoya, DO FACOI FCCP FAASM
Christiana Care Pulmonary Associates
Clinical Assistant Professor of Medicine
Sidney Kimmel Medical College of Thomas Jefferson University
Rowan University School of Osteopathic Medicine

ACOI Board Review 2019

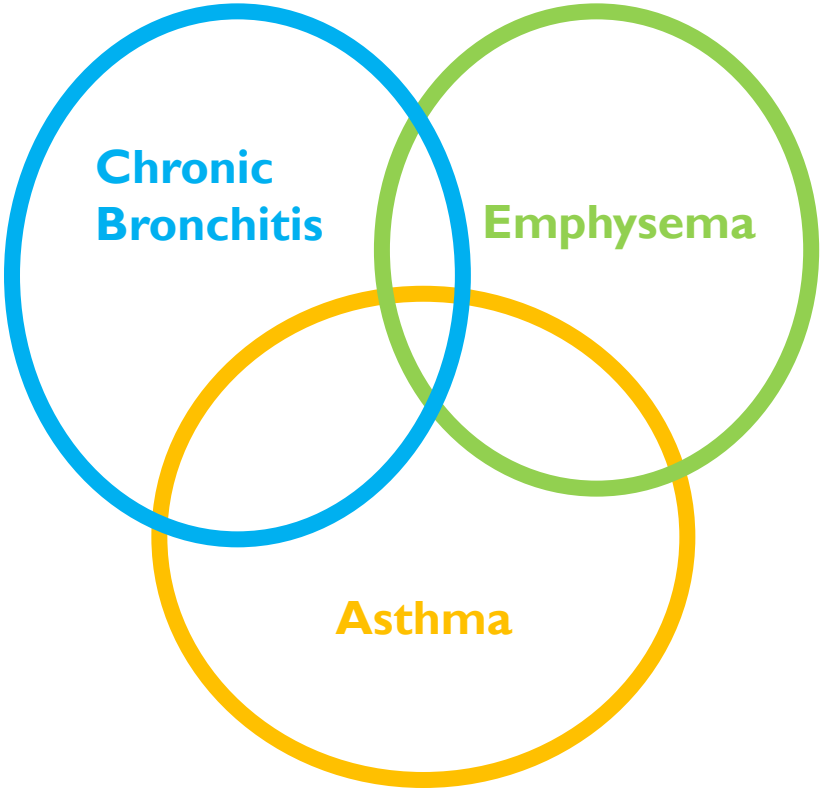
American College of Osteopathic Internists

Disclosures

- No Disclosures

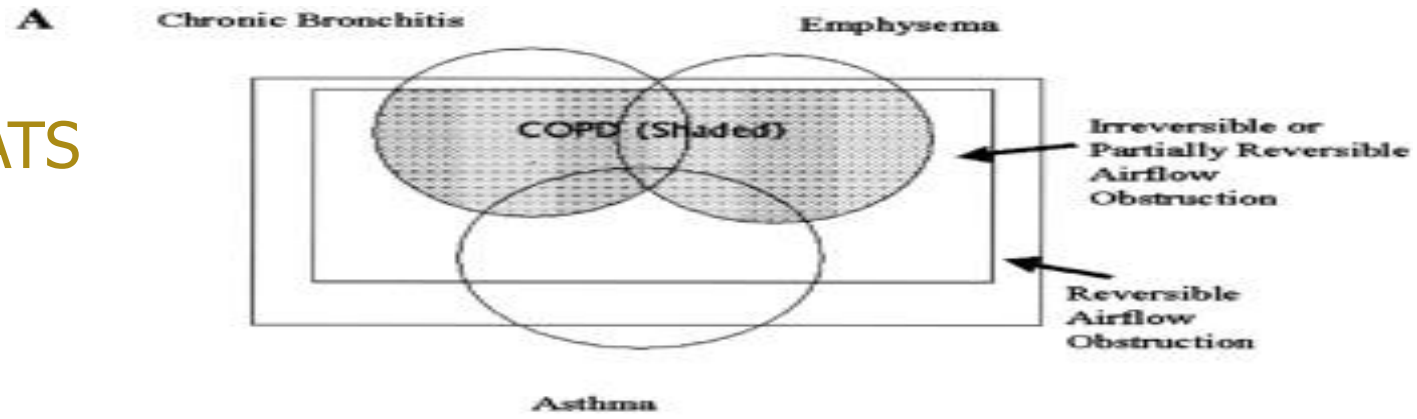
Obstructive Lung Diseases

- COPD
  - Chronic Bronchitis
  - Emphysema
- Asthma
- Other
  - Bronchiectasis
  - Bronchiolitis
  - Cystic Fibrosis
  - Alpha 1 anti-trypsin deficiency

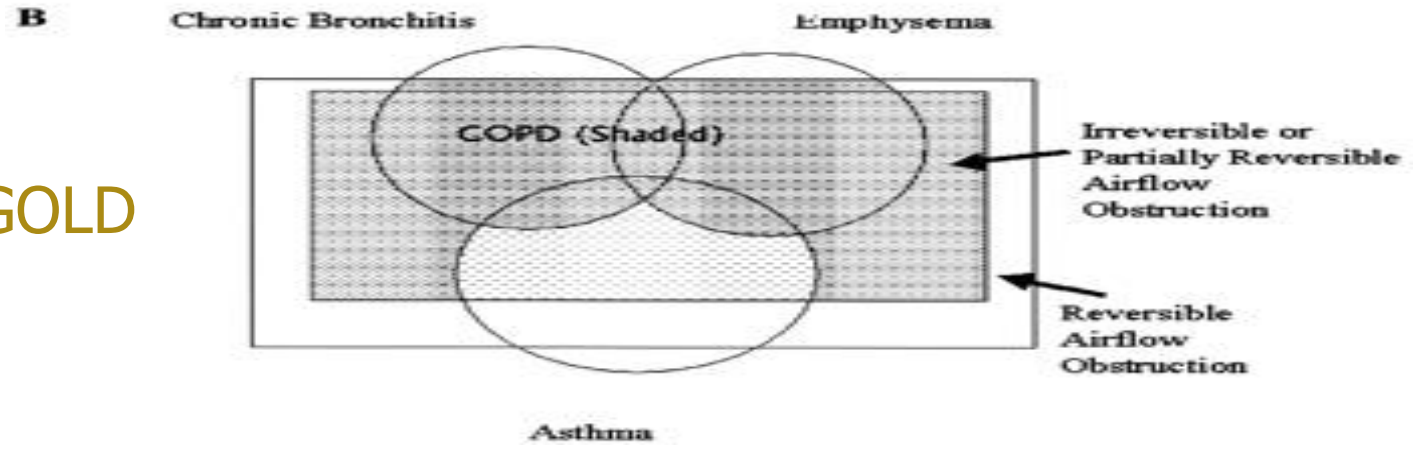


Inter-relationship: Inflammation and Bronchial Hyperreactivity

ATS



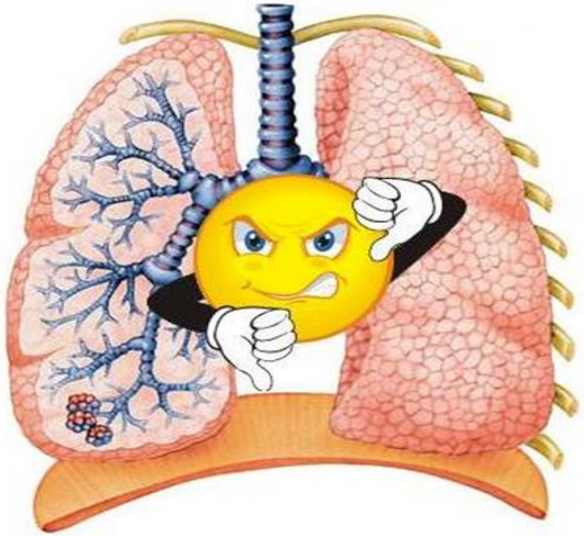
GOLD

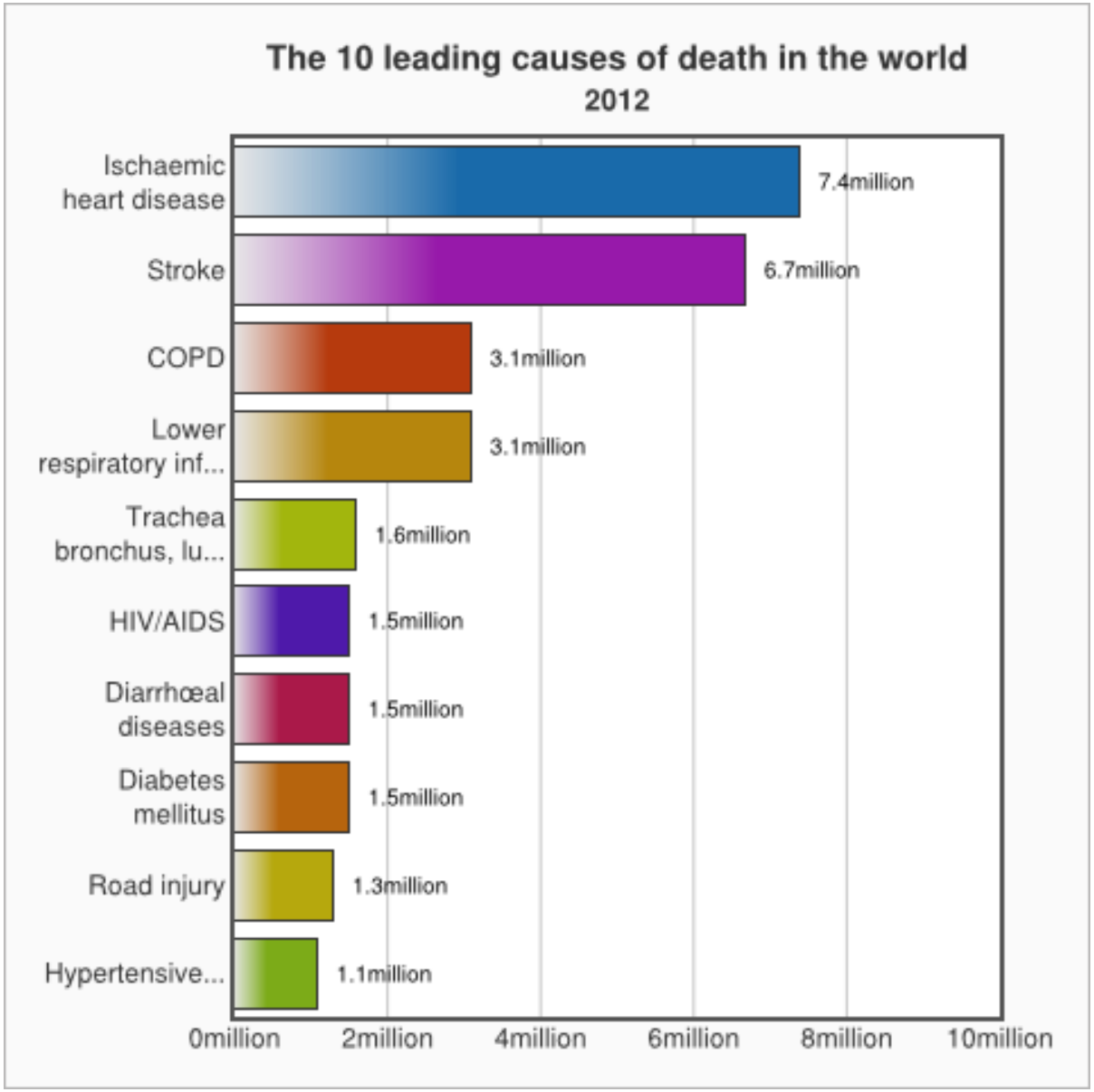


CHEST 2002; 121: 121S-126S

COPD

- THIRD leading cause of death worldwide
- It is the only leading cause of death whose prevalence is increasing!





http://www.who.int/mediacentre/factsheets

COPD Risk Factors

- Cigarette smoking
- Occupational exposures
  - Silica, formaldehyde, toluene, nickel, cadmium, cotton, dust, etc
- Air pollution
- Biomass fuel
- Hyperresponsive airway
- Asthma
- Genetic factors

Pathogenesis of COPD

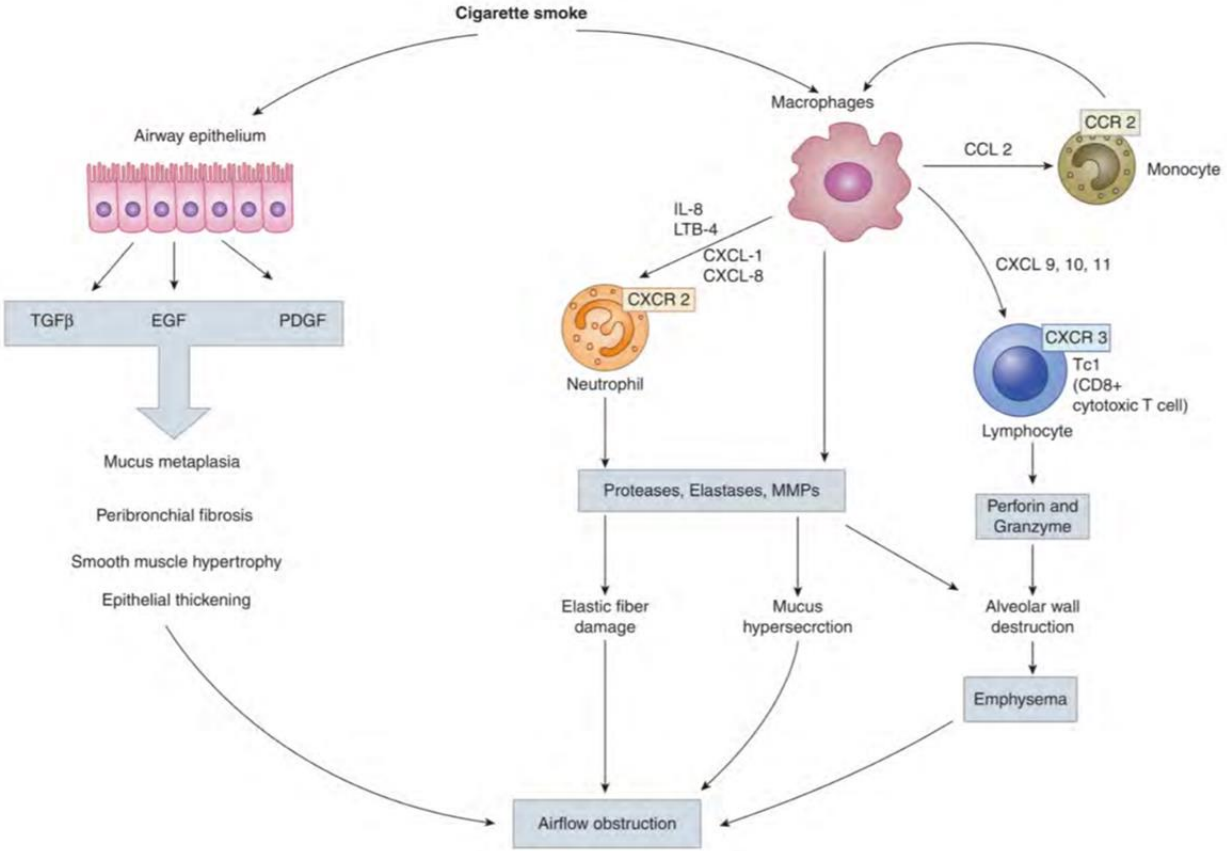


Figure 3-13. Macrophages are activated by cigarette smoke and recruit neutrophils and CD+ lymphocytes to cause elastolysis and emphysema. Similarly, cigarette smoke activates airway epithelium to trigger airway remodeling. Both of these processes result in airflow obstruction.

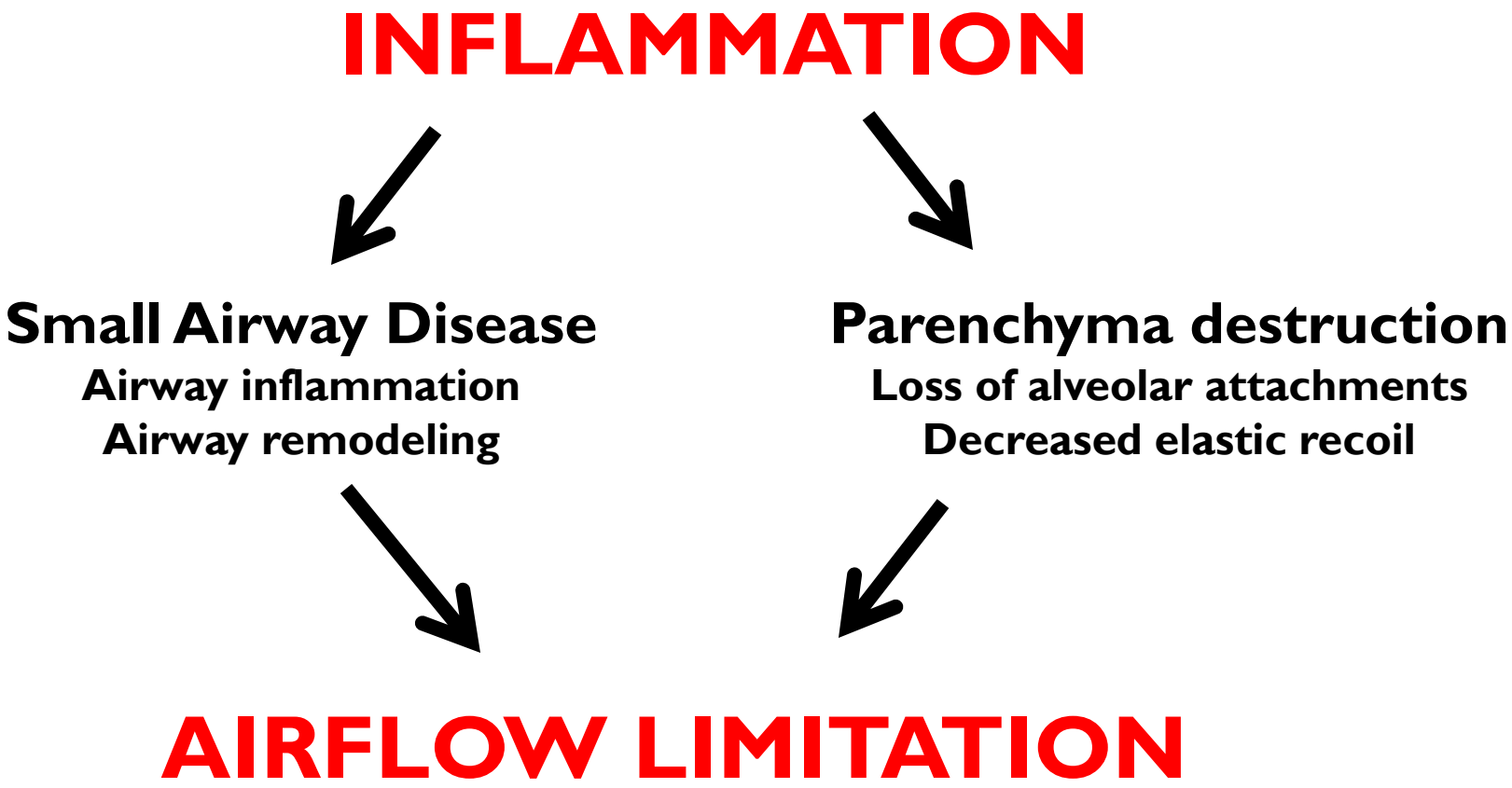
CXCR3, chemokine CXC receptor 3; CXCR2, chemokine CXC receptor 2; EGF, epidermal growth factor; IL-8, interleukin 8; CXCL, CXC chemokine ligand; CCL, CC chemokine ligand; LTB4, leukotriene B4; MMPs, matrix metalloproteinases; PDGF, platelet-derived growth factor; TGF β, transforming growth factor β.

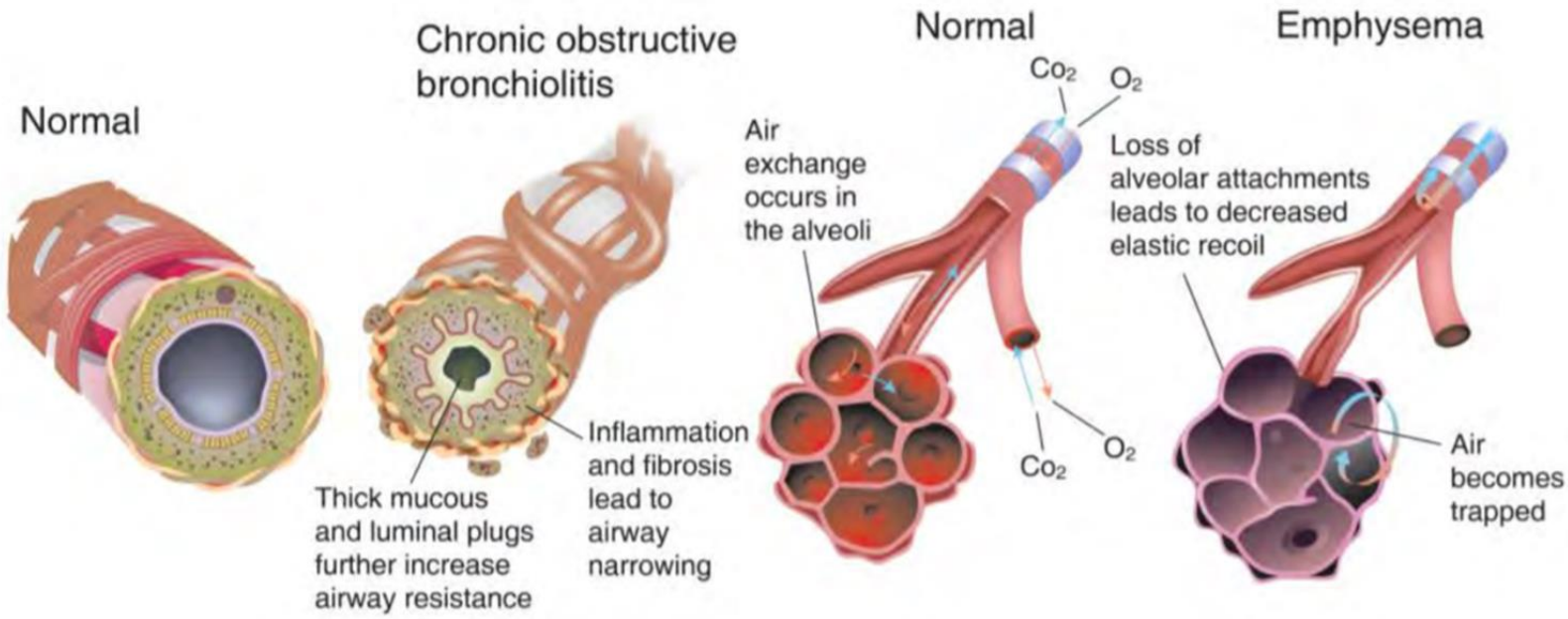
ATS Pulmonary Board Review 2015

Inflammatory Mediators: COPD

Table 3-23. Overview of Asthma and COPD Pathogenesis

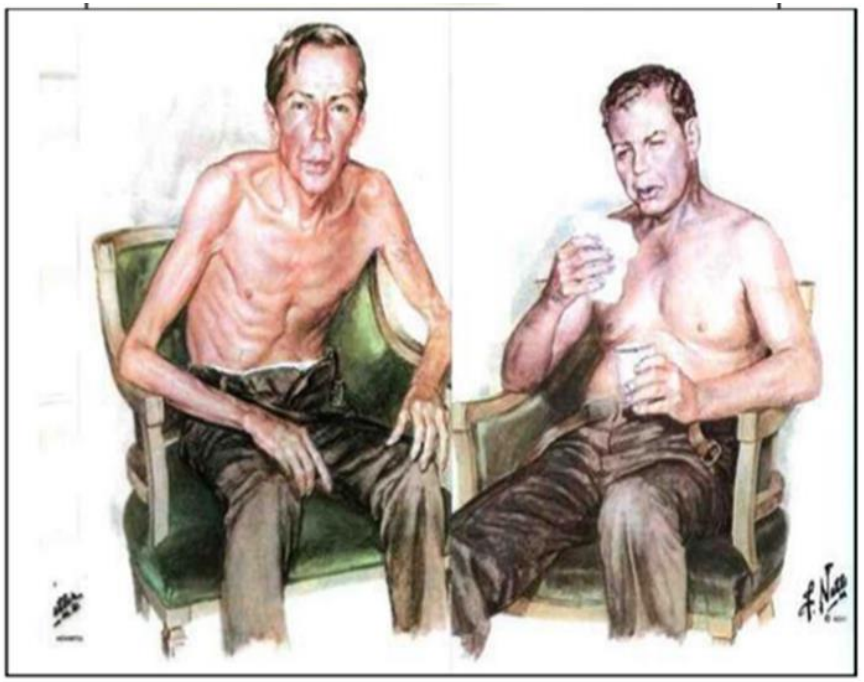
Feature	Asthma	COPD
Inciting factor	Allergen or irritant	Smoking or irritant
Major cell types	Epithelial cells, T_h2 cells (CD4+) Mast cells, eosinophils	T_h1 and T_C1 cells (CD8+) Neutrophils, macrophages
Mediators	IL-4, IL5, IL-13	LTB4, TNFα, IL-8
Airway and parenchymal involvement	Mainly large airway No parenchymal involvement	Small airway fibrosis Parenchymal destruction
Pathological changes	Subepithelial fibrosis Smooth muscle hyperplasia+++ Mucous metaplasia Basement membrane thickening	Peribronchial fibrosis Smooth muscle hyperplasia+ Mucous metaplasia Alveolar destruction
Airflow limitation	**Reversible** **Airflow limitation** **Partially reversible**	


INFLAMMATION
Small Airway Disease
Airway inflammation
Airway remodeling
Parenchyma destruction
Loss of alveolar attachments
Decreased elastic recoil
AIRFLOW LIMITATION

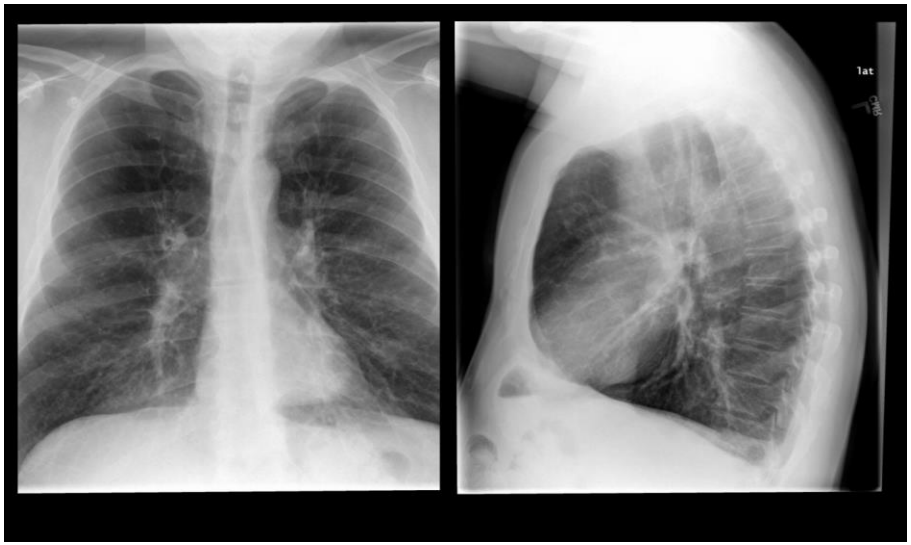

Normal
Chronic obstructive bronchiolitis
Thick mucous and luminal plugs further increase airway resistance
Inflammation and fibrosis lead to airway narrowing
Normal
Air exchange occurs in the alveoli
Co2
O2
Co2
O2
Emphysema
Loss of alveolar attachments leads to decreased elastic recoil
Air becomes trapped

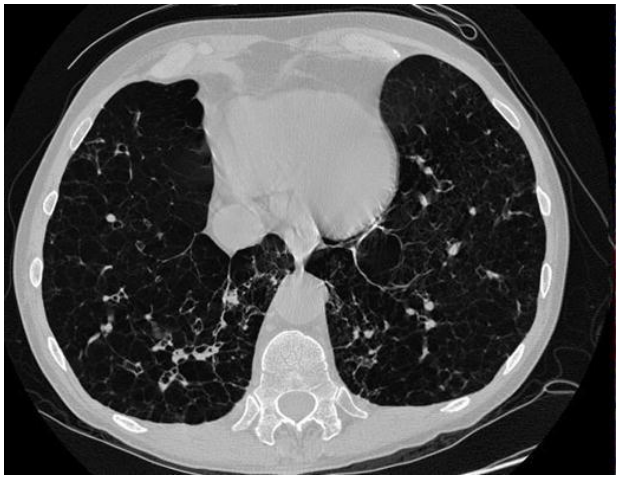
COPD Phenotypes

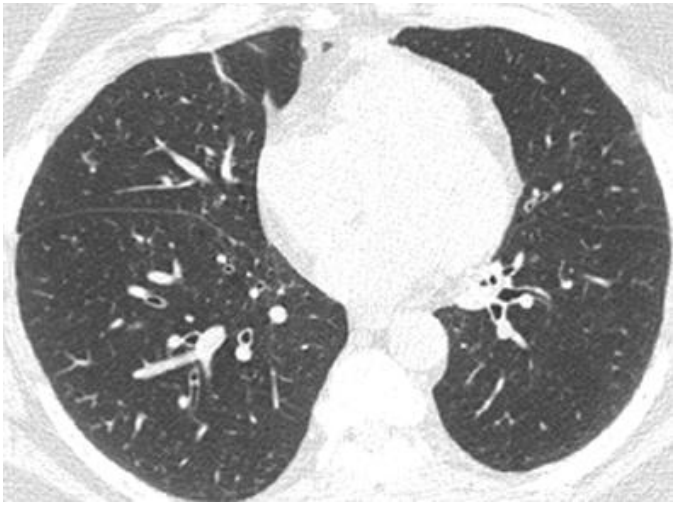
- Non-exacerbator
- Exacerbator with emphysema
- Exacerbator with chronic bronchitis
- Frequent exacerbator
- Alpha 1 Antitrypsin deficiency
- ACOS
- BCOS



www.eclipse-copd.com,
Lange P. Int J COPD 2016. 11: 3-12
Hurst JR. NEJM 2010. 363: 1128-38


lat

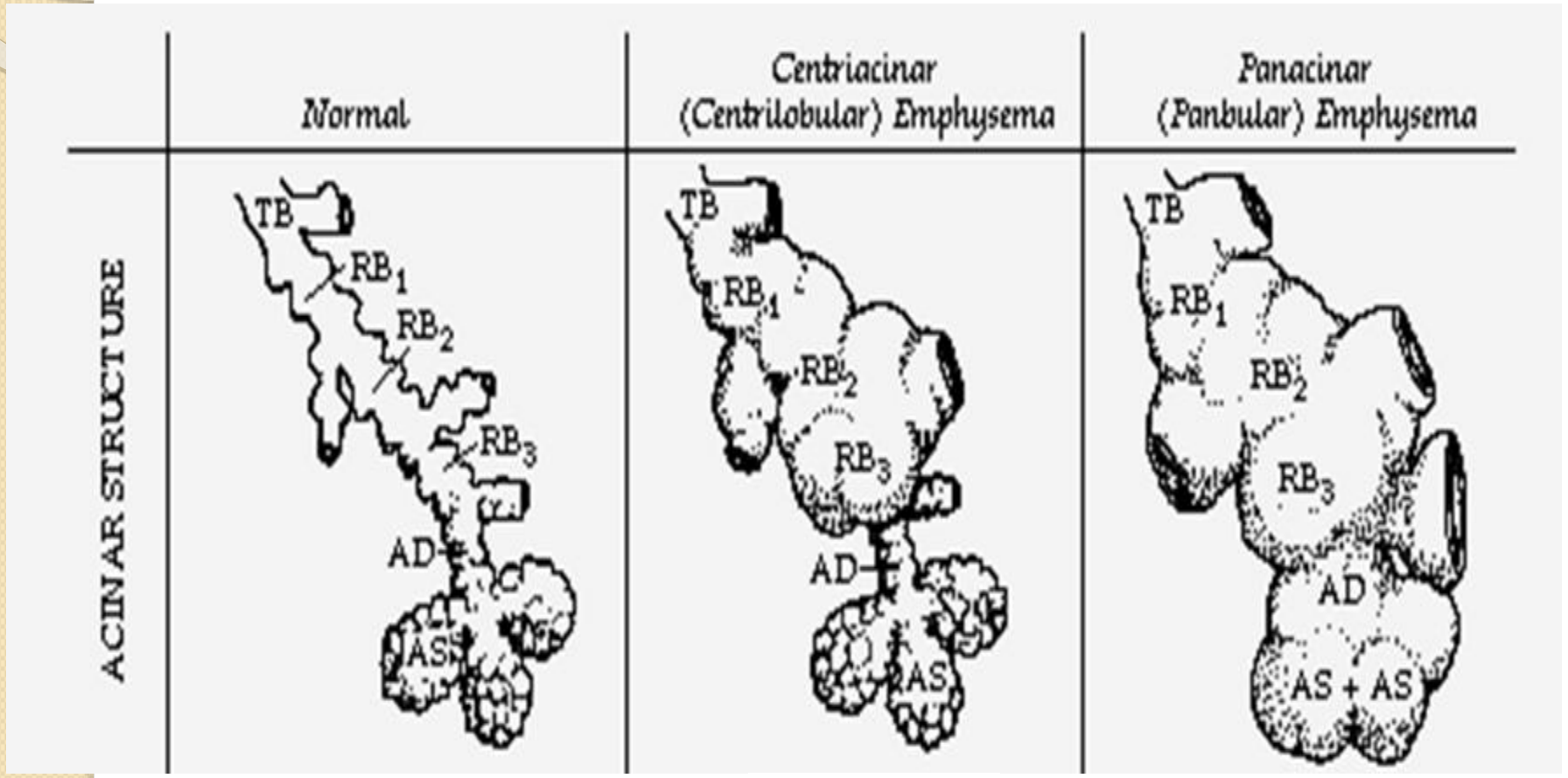




Morphologic Types of Emphysema

Upper lobe

Lower lobe



Alpha 1 AT

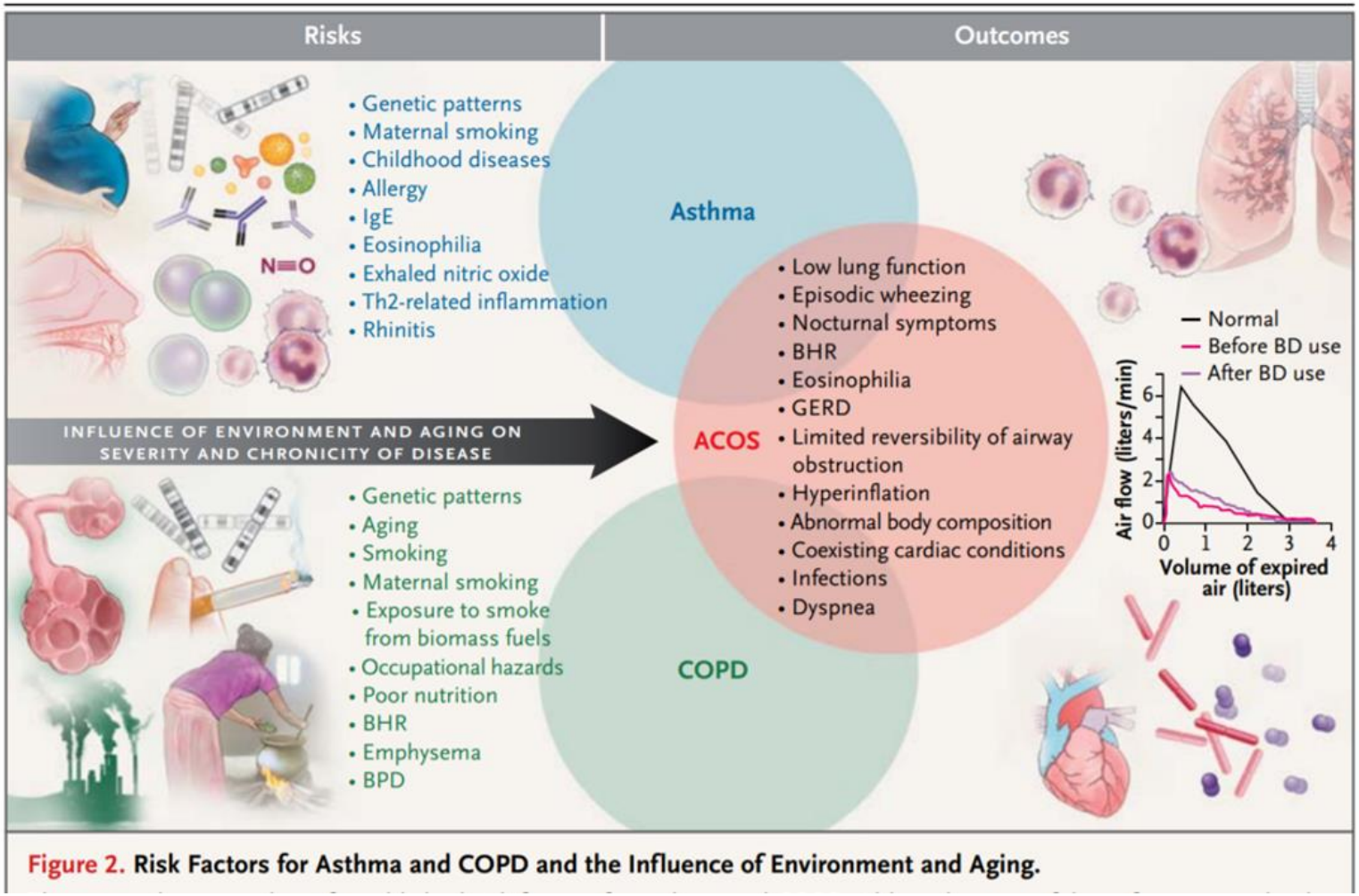
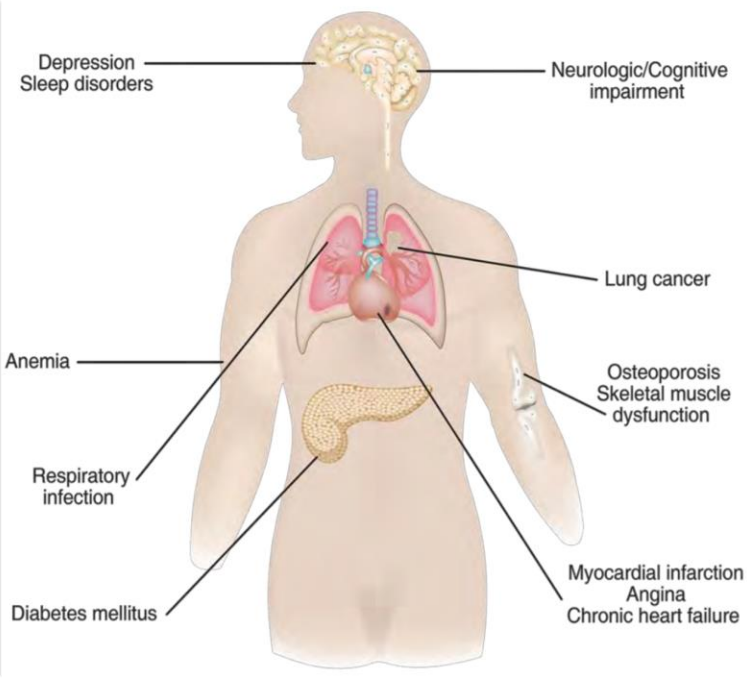


Figure 2. Risk Factors for Asthma and COPD and the Influence of Environment and Aging.

Postma DS, Rabe KF. NEJM 2015. 373:1241-49

COPD Diagnosis

- Clinical presentation
- Risk Factors
- Pulmonary function testing
- Imaging
- Resting/ambulatory pulse ox
- ABG
- Alpha 1 antitrypsin deficiency screen



COPD Definition: GOLD

- Chronic Obstructive Pulmonary Disease (COPD) is a PREVENTABLE and TREATABLE disease with some significant extrapulmonary effects that may contribute to the severity in individual patients
- Airflow limitation that is NOT fully reversible
- Airflow limitation is usually persistent and progressive
- Associated with an abnormal inflammatory response to noxious particles and gases

COPD Definition: GOLD

- A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease.

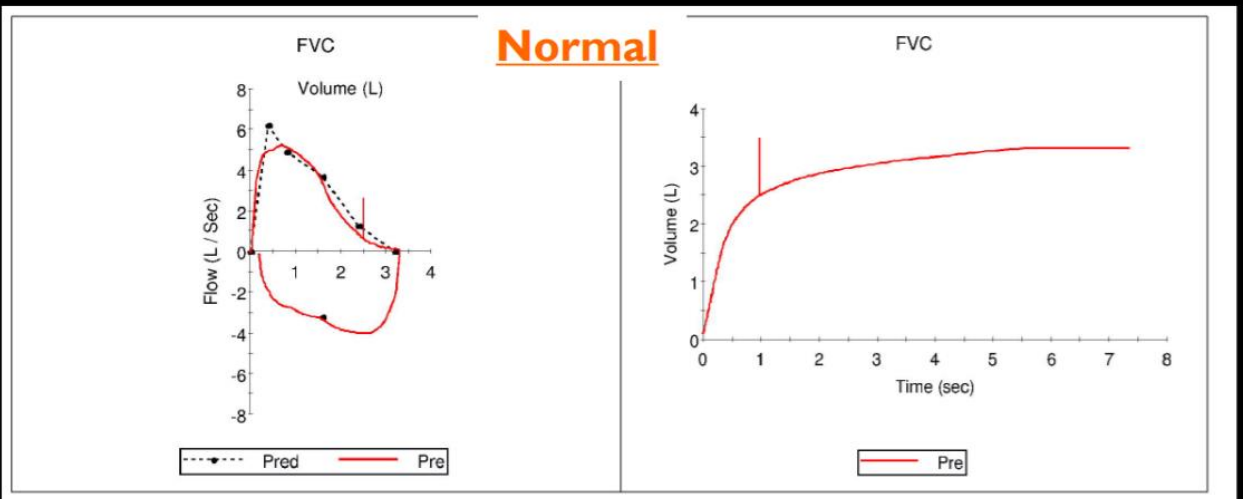
- Spirometric evaluation is necessary for the clinical diagnosis.

COPD Definition: GOLD

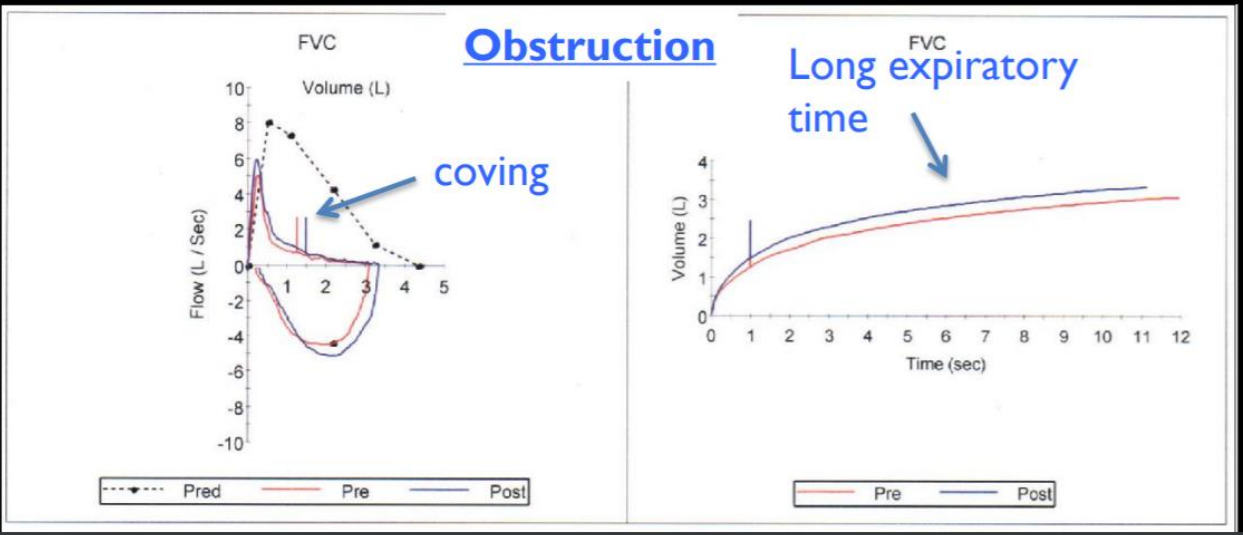
- A post bronchodilator FEV1/FVC <70%
- In combination with an FEV1 <80% predicted
- In an individual with cough, sputum production or dyspnea, and exposure to risk factors confirms the diagnosis

www.goldcopd.org

Normal



Obstruction



	% predicted
FEV1	>80
FVC	>80
FEV1/FVC	>90

FEV1/FVC	<LLN OR <70%

Severity of COPD: GOLD

Stage	Severity	FEV1/FVC	FEV1 (%PRED)
1	Mild	< 70%	80% or >
2	Moderate	< 70%	50 to 79%
3	Severe	< 70%	30 to 49%
4	Very Severe	< 70%	< 30% or < 50 with CRF

www.goldcopd.org

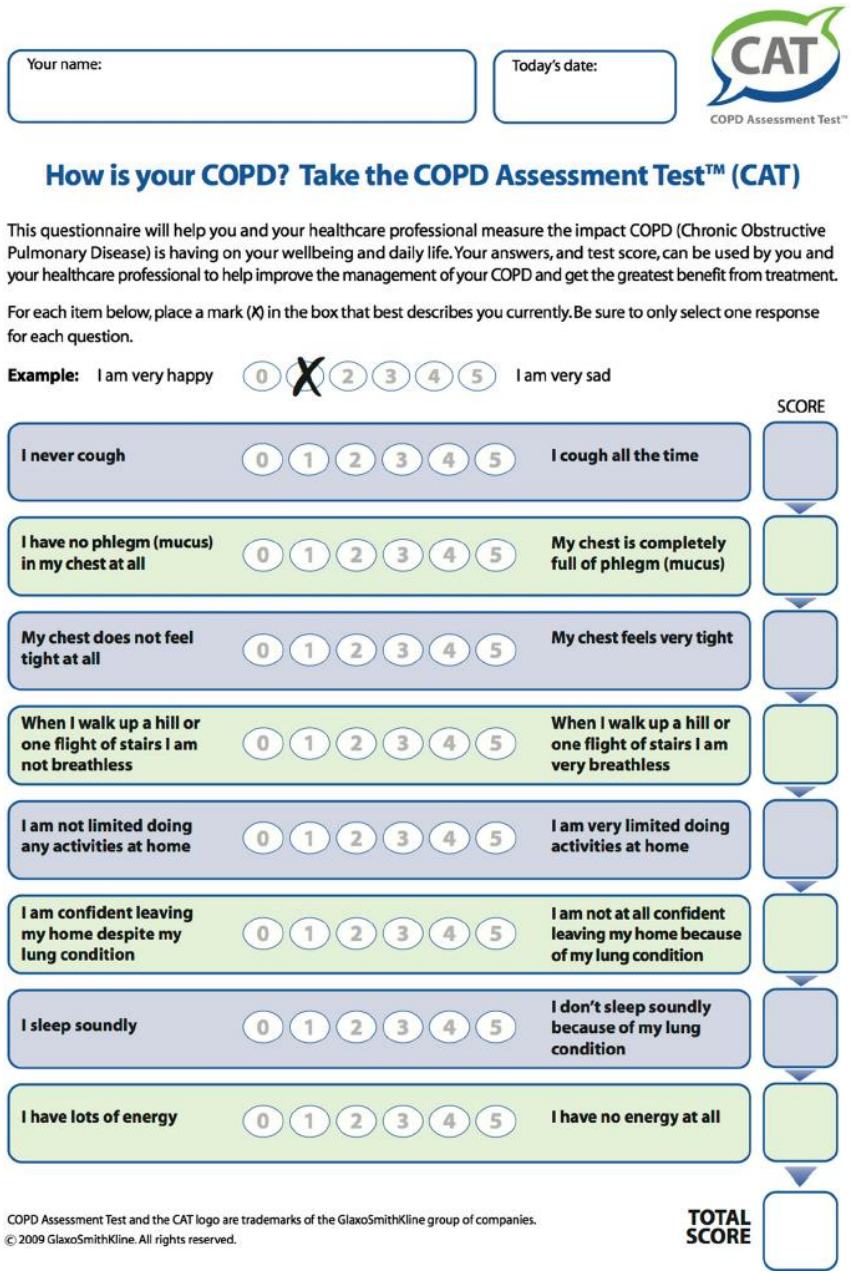
Definition of Reversibility

ATS	Increase in FEV1 of 200 cc and a 12% from baseline following BD
ERS	Greater than 10% improvement in FEV1 post BD
GOLD	Increase in FEV1 of 200 cc and a 12% improvement in FEV1 post Tx with either BD or ICS

Assessment

- CAT (COPD Assessment Test)
  - Numeric scale relating 8 functional parameters
    - Cough, sputum, walking, sleeping, energy, etc
  - Lower score=fewer symptoms
  - Higher score=more symptoms
- mMRC Questionnaire (Modified Medical Research Council)
  - Degree of breathlessness using 0-4 scale
  - Higher values indicating decreasing exercise tolerance

CAT



Your name:

Today's date:

CAT
COPD Assessment Test™

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

TOTAL SCORE

mMRC Questionnaire

Modified Medical Research Council (mMRC) Questionnaire for Assessing Severity of Breathlessness

Score	Description of Dyspnea	Severity
0	I get breathless only with strenuous exercise	None
1	I get short of breath when hurrying on level ground or walking up a slight hill	Mild
2	On level ground, I walk slower than other people my age because of breathlessness, or I have to stop for breath when walking at my own pace	Moderate
3	I stop for breath after walking approximately 100 yards or after a few minutes on level ground	Severe
4	I am too breathless to leave the house, or breathless when dressing	Very severe

GOLD: Severity of COPD

GOLD Model for Classifying Severity of Disease in COPD

Patient Category	Characteristics	Spirometric Classification[a]	Exacerbations Per Year	CAT Score	mMRC Score
A	Low risk, fewer symptoms	GOLD 1-2	≤1	<10	0-1
B	Low risk, more symptoms	GOLD 1-2	≤1	≥10	≥2
C	High risk, fewer symptoms	GOLD 3-4	≥2	<10	0-1
D	High risk, more symptoms	GOLD 3-4	≥2/≥1 with hospital admission	≥10	≥2

CAT = COPD Assessment Test; mMRC = Modified Medical Research Council.

Diagnostic Techniques

- History/Physical (symptoms – more sensitive)
- Pulmonary Function Testing
- Imaging: CXR, Chest CT, V/Q scan
- Pulse oximetry at rest and with activity
- ABG
- Alpha 1 Antitrypsin Deficiency Screen
  - COPD in caucasian under age 45 y or with strong family history of COPD

Reasons for delay in Diagnosis

- Patient does not seek medical attention until late in disease process (ie emphysema)
- Physicians focus on treatment of symptoms rather than disease prevention
- We may be looking at the wrong thing (waiting too long until PFT, x-rays, spirometry, etc are abnormal).

Systemic Features of COPD

- Cachexia: loss of fat free mass
- Skeletal muscle wasting: apoptosis, disuse atrophy
- Osteoporosis
- Depression
- Normochromic normocytic anemia
- Increased risk of cardiovascular disease

Exercise limitation

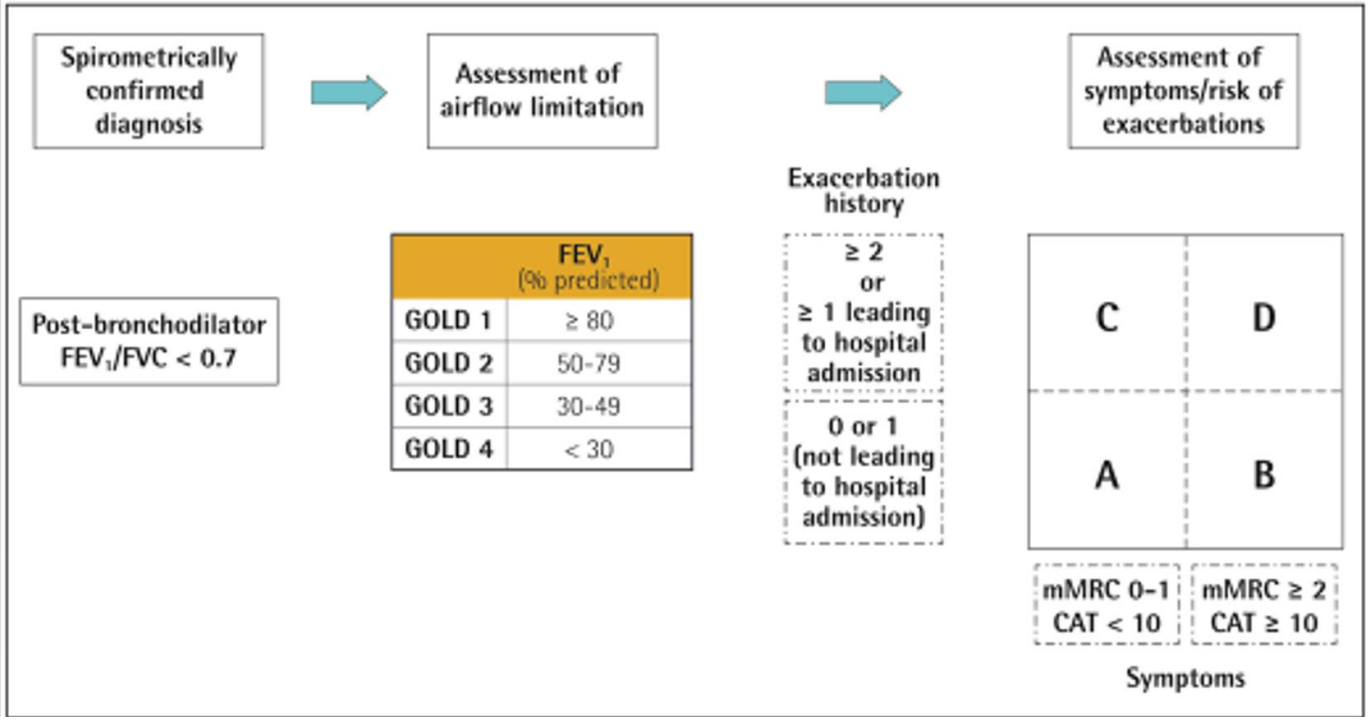
- Normal individuals never reach a respiratory limitation at peak exercise
- However COPD patients have a reduced maximum ventilation and this can limit there exercise capacity
- These patients can have airflow limitation to exercise
- They can also desaturate with exercise

COPD Treatment: Goals

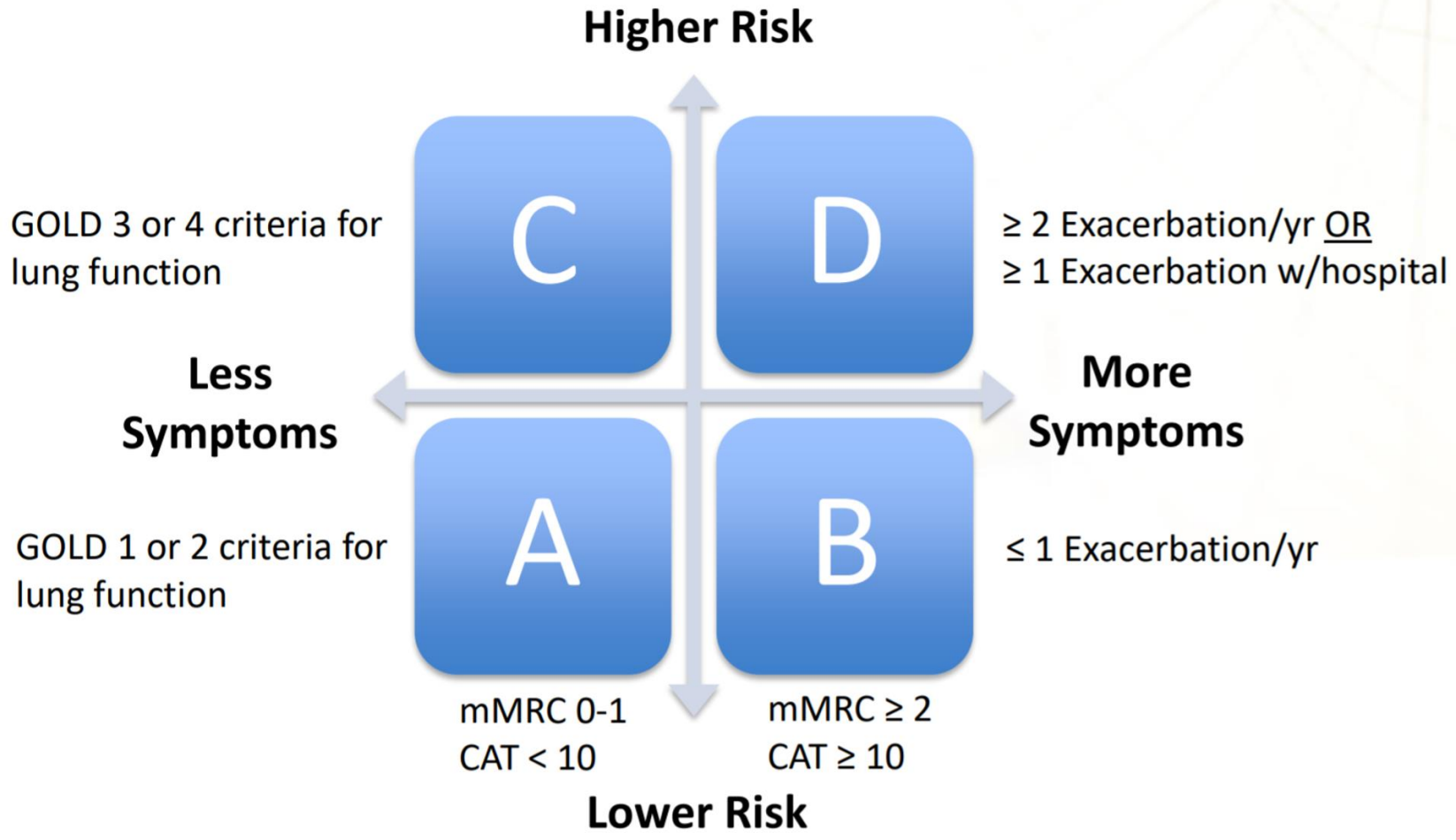
- Slow disease progression
- Reduce the frequency and severity of disease exacerbations
- Improve quality of life

Table 2.4. Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV_1)		
In patients with $FEV_1/FVC < 0.70$:		
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

Figure 2.4. The refined ABCD assessment tool



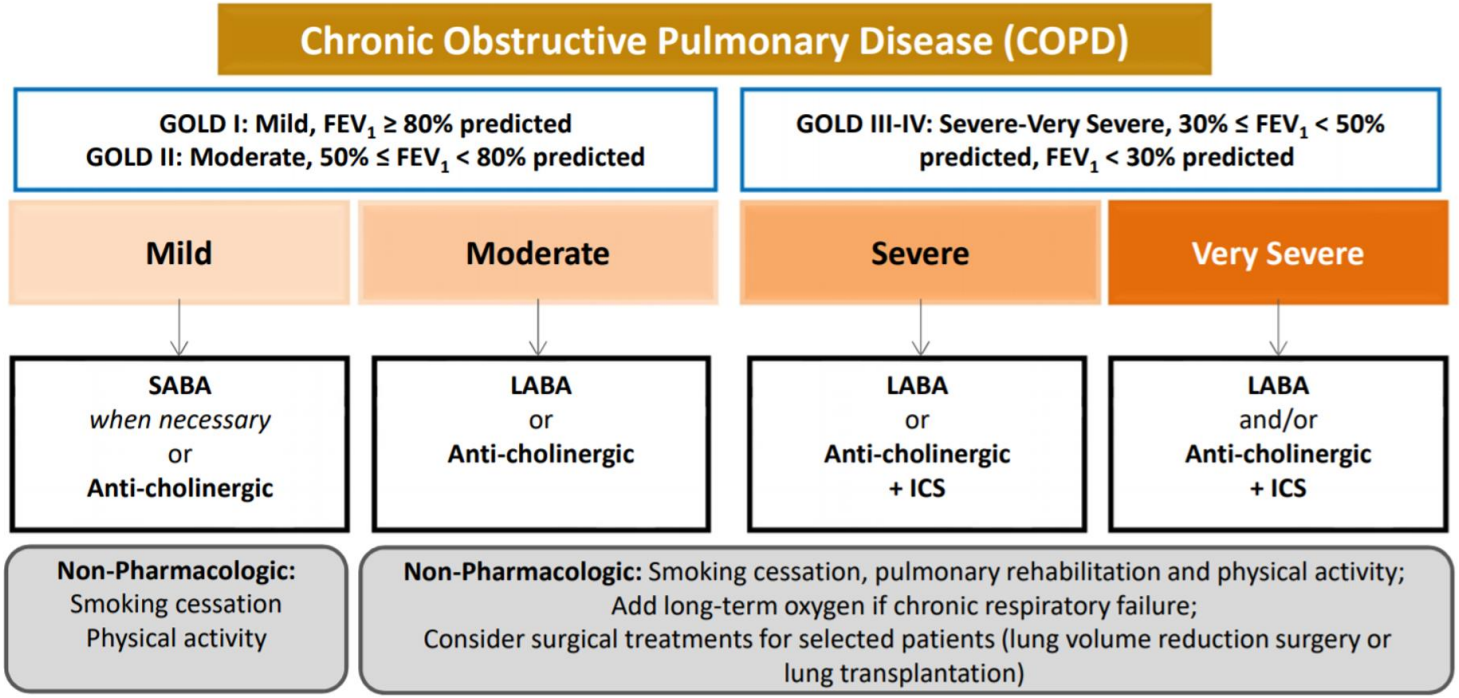
www.goldcopd.org 2017



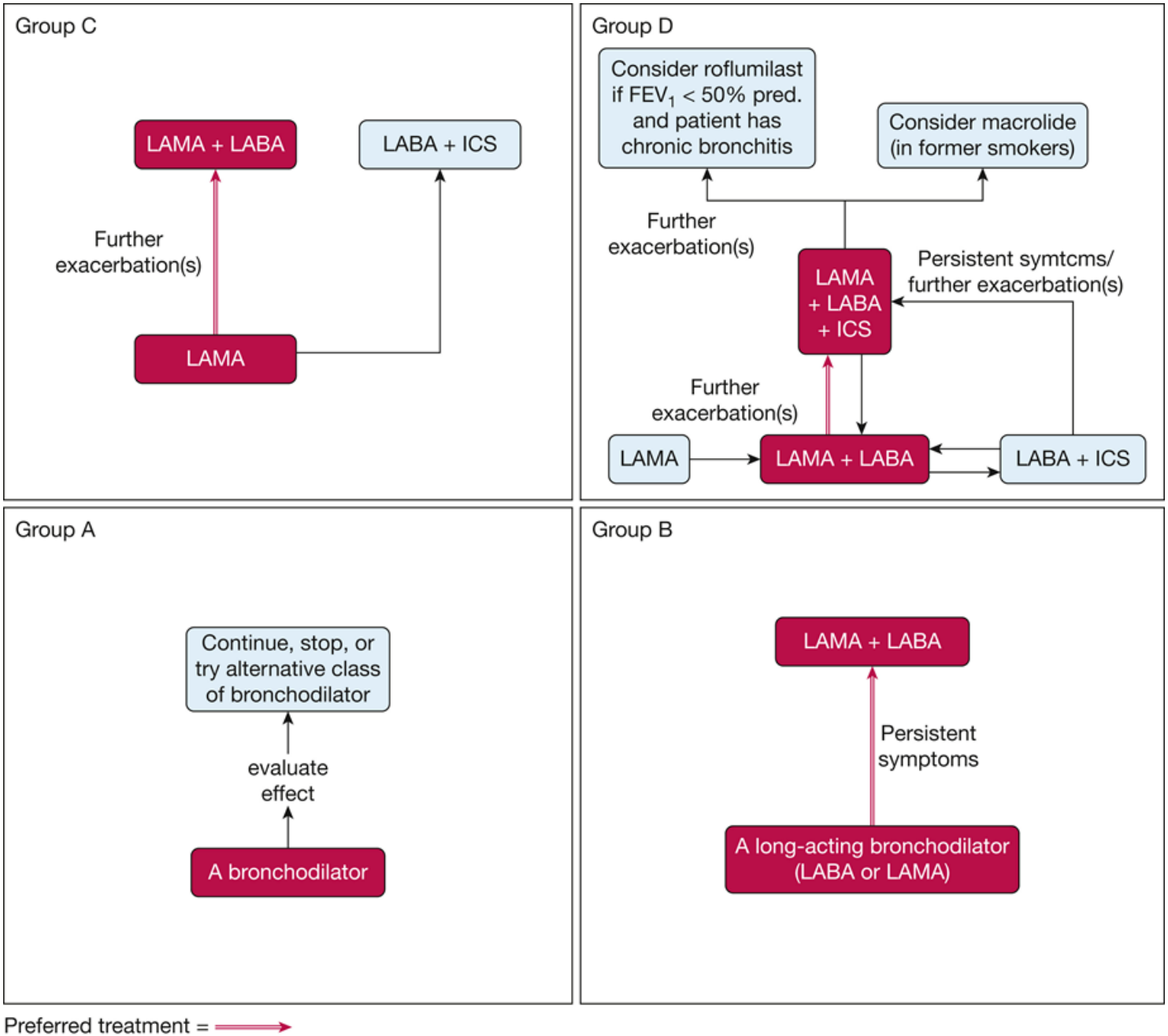
CAT = COPD Assessment Test; mMRC = modified Medical Research Council Dyspnea Scale

www.goldcopd.org 2017
Lee H et al. Am Fam Phys. 2013. 88(10):655-663

GOLD Guidelines: Changing Paradigm



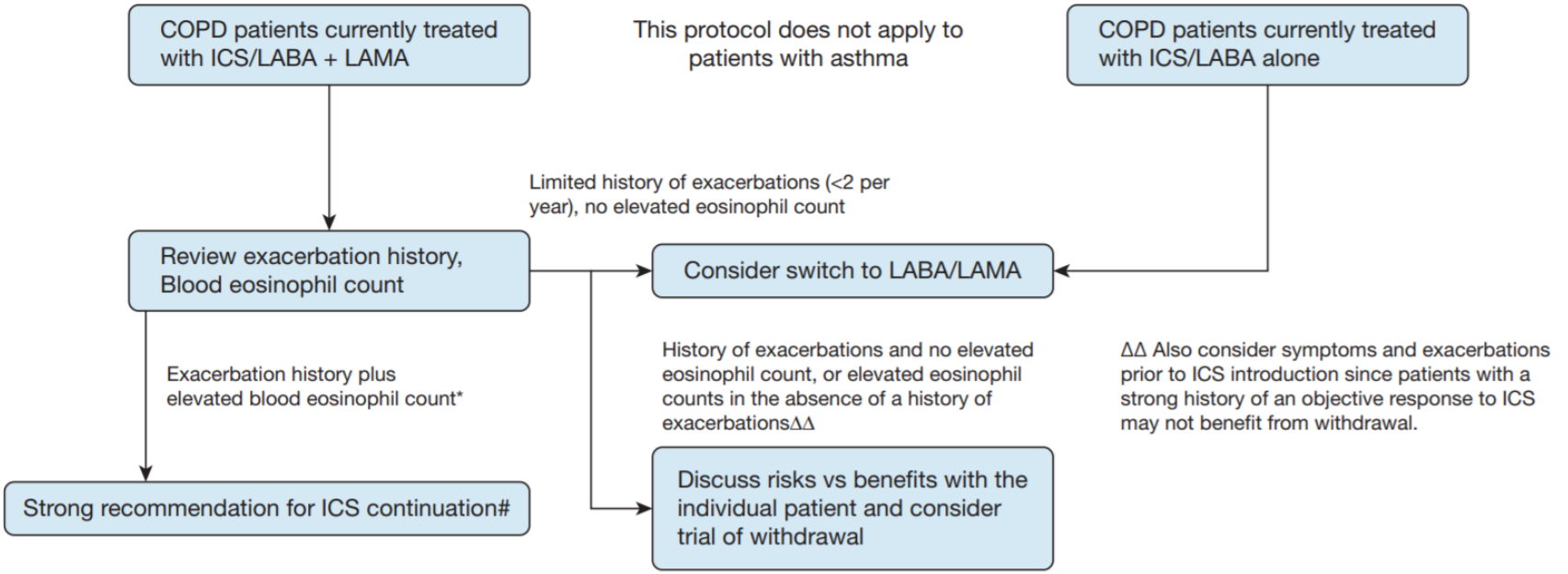
Source: Cowen Report, March 2017; American Lung Association; Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.



Chalmers JD. CHEST 2018. 153(4):778-782

Clancy and Heath. Univ Penn.
www.thoracic.org

Consideration for ICS Withdrawal



*Consider blood eosinophil counts as supporting evidence when discontinuing inhaled corticosteroids. A blood eosinophil count <300 cells per ul adds additional confidence that ICS is not required. Note that oral corticosteroids suppress blood eosiniphil counts and so values taken during or after a recent course of oral corticosteroids may not be reliable.

#patients with frequent exacerbations should be reviewed to include underlying co-morbidities (asthma/bronchiectasis), and to optimise treatment (pulmonary rehabilitation, inhaler technique)

Chalmers JD. CHEST 2018. 153(4):778-782

Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β_2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE^{2}SPOND). A Randomized Clinical Trial

Fernando J. Martinez [1], Klaus F. Rabe [2,3,4], Sanjay Sethi [5], Emilio Pizzichini [6], Andrew McIvor [7], Antonio Anzueto [8,9], Vijay K. T. Alagappan [10], Shahid Siddiqui [10], Ludmyla Rekeda [11], Christopher J. Miller [10], Sofia Zetterstrand [12], Show

CONCLUSION:
Roflumilast failed to statistically significantly reduce moderate and/or severe exacerbations in the overall population. Roflumilast improved lung function and reduced exacerbations in participants with frequent exacerbations and/or hospitalization history.
The safety profile of roflumilast was consistent with that of previous studies.

SE: depression, anxiety, suicidal thoughts, weight loss;
drug-drug interactions: erythromycin, ketoconazole, cimetidine

Do not use with theophylline; can use with azithromycin
Limited role in severe copd. No role in mild-moderate disease

DO NOT USE IN ACUTE SETTING

Martinez FJ et al. AJRCCM 2016. 194(5)

Azithromycin

- Azithromycin 250 mg taken daily for 1 year when added to usual treatment, decreased the frequency of exacerbations and improved quality of life
- Risk of cardiovascular death (underlying CAD)
- Check baseline QTc
- Hearing impairment
- Antibiotic resistance
- Review of 350K prescriptions to patients without severe cardiac disease v no antibiotic use
  - Absolute increase in cardiac death in 29 (1 in 20,000)

Albert, RK. et al. NEJM 2011. 365(8): 689-698.
Ray WA. NEJM 2012. 366: 1881-1890

Medication side effects: SABA/SAMA

Bronchodilators		
Inhaled short-acting β_2-agonists (albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol, terbutaline)	Tachycardia and hypokalemia (usually dose dependent), but generally well tolerated by most patients	Generally used as needed for mild disease with few symptoms
Inhaled short-acting anticholinergic agents (ipratropium)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma; this drug class has been shown to be safe in a wide range of doses and clinical settings	Not to be used with tiotropium; generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics

Medication side effects: LABA/LAMA

Inhaled long-acting anticholinergic agents (tiotropium, aclidinium, umeclidinium, glycopyrronium)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma	Not to be used with ipratropium; use when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV_1 <60% of predicted
Inhaled long-acting β_2-agonists (salmeterol, formoterol, arformoterol, indacaterol, olodaterol)	Sympathomimetic symptoms such as tremor and tachycardia; overdose can be fatal	Use as maintenance therapy when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV_1 <60% of predicted; not intended to be used for treatment of exacerbations of COPD or acute bronchospasm

ACP MKSAP 2017

Medication side effects: Methylxanthines/Oral B2 agonists

Methylxanthines (theophylline, aminophylline; sustained and short-acting)	Tachycardia, nausea, vomiting, disturbed pulmonary function, and disturbed sleep; narrow therapeutic index; overdose can be fatal with seizures and arrhythmias	Used as maintenance therapy; generally use only after long-acting bronchodilator treatment to provide additional symptomatic relief of exacerbations; may also improve respiratory muscle function
Oral β_2-agonists (albuterol, metaproterenol, terbutaline)	Sympathomimetic symptoms such as tremor and tachycardia	Used as maintenance therapy; rarely used because of side effects but may be beneficial for patients who cannot use inhalers

Medication side effects: Roflumilast

Oral Phosophodiesterase-4 Inhibitor		
Roflumilast	Diarrhea, nausea, backache, decreased appetite, dizziness	Used to reduce risk for exacerbations in patients with severe COPD (blood levels not required) with chronic bronchitis and history of exacerbations; roflumilast should not be used with methylxanthines owing to potential toxicity; very expensive and should be used only in select patients

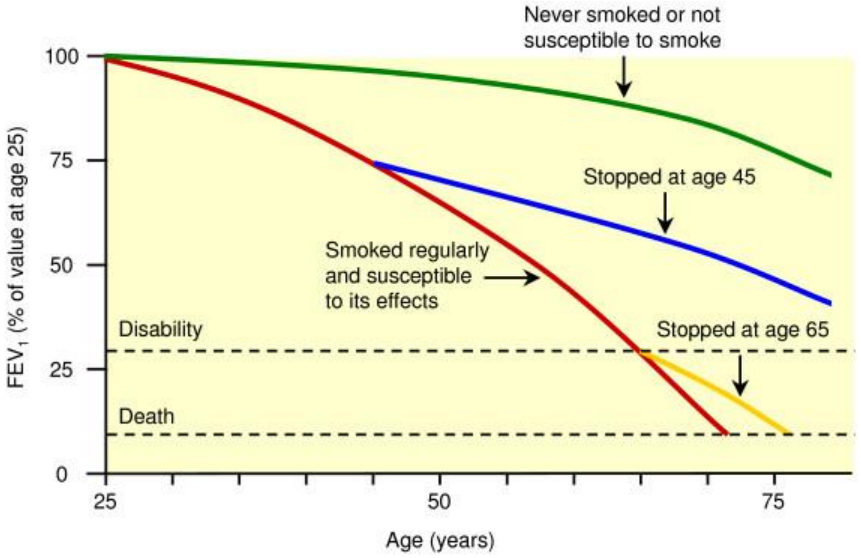
Medication side effects: Inhaled/Oral glucocorticoids

Anti-Inflammatory Agents		
Inhaled glucocorticoids (fluticasone, budesonide, mometasone, ciclesonide, beclomethasone)	Dysphonia, skin bruising, oral candidiasis, rarely side effects of oral glucocorticoids (see below)	Most effective in patients with a history of frequent exacerbations and when used in conjunction with long-acting bronchodilators; not approved by the FDA for treatment for COPD
Oral glucocorticoids (prednisone, prednisolone)	Skin bruising, adrenal suppression, glaucoma, osteoporosis, diabetes mellitus, systemic hypertension, pneumonia, cataracts, opportunistic infection, insomnia, mood disturbance	Use for significant exacerbations of COPD with taper; avoid, if possible, in stable COPD to limit glucocorticoid toxicity; consider inhaled glucocorticoids to facilitate weaning of systemic glucocorticoids

ACP MKSAP 17

Nonpharmacologic Treatment

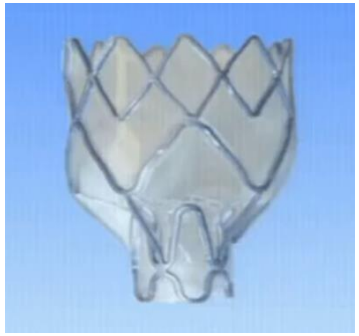
- **SMOKING CESSATION**
- Patient education
- Medication compliance
- Pulmonary rehabilitation
- Vaccination
- Nutritional support
- Oxygen therapy
- Consider lung volume reduction surgery
- Consider endobronchial valve placement
- Consider lung transplant
- End of life/palliative care



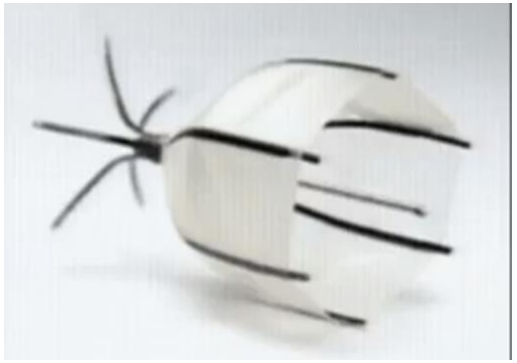
Fletcher C. and Peto R. BMJ. 1977. 1:1645

LVRS/Valves

- LVRS
  - Surgically remove damaged lung
    - Reduce dead space,
    - Improve respiratory dynamics
  - No overall survival advantage, except for upper lobe disease and poor exercise capacity



- Endobronchial valves
  - Permit exhalation/drainage of secretions but no air entry with inspiration
  - Zephyr valve FDA approved 2018
  - Increased FEV1/6min walk
  - Pneumonia, AECOPD, hemoptysis



Sciurba FC NEJM 2010. 363:1233

Lung Transplant in COPD

- Improves exercise tolerance/QOL
- Consider referral
  - Age <70, smoke free (min 6 mo)
  - Poor functional status
  - BODE index >5
  - FEV1<25%, DLCO <25%
  - Resting hypoxemia, hypercapnia
  - PHTN
- Median survival
  - 4-7 years
- Single or double lung transplant
- Complications with transplant
  - Rejection
  - Infection

www.uptodate.com

Assess COPD Comorbidities

- Cardiovascular disease
- Osteoporosis
- Respiratory infections
- Anxiety and Depression
- Diabetes
- LUNG CANCER

These comorbid conditions influence mortality and hospitalizations; and should be looked for routinely and treated appropriately

Asthma

Asthma

- Definition:
  - Chronic inflammatory disorder of the airways triggered by various sensitizing stimuli resulting in reversible airflow obstruction
- Key Components:
  - Airway hyperresponsiveness
  - Airflow limitation
    - Bronchoconstriction, mucus plugs, inflammation, thickening of the basement membrane, increased smooth muscle mass
- Symptoms: episodic or persistent
  - Dyspnea, wheezing, cough, chest tightness
  - Diurnal variation (night and early morning)
- Genetic factors: no single derangement, sex and obesity
- Environmental factors:
  - Allergens (dust, pollen, dander, mold), viruses, occupational exposures, tobacco smoke, air pollution, biomass fuel

Asthma Classification

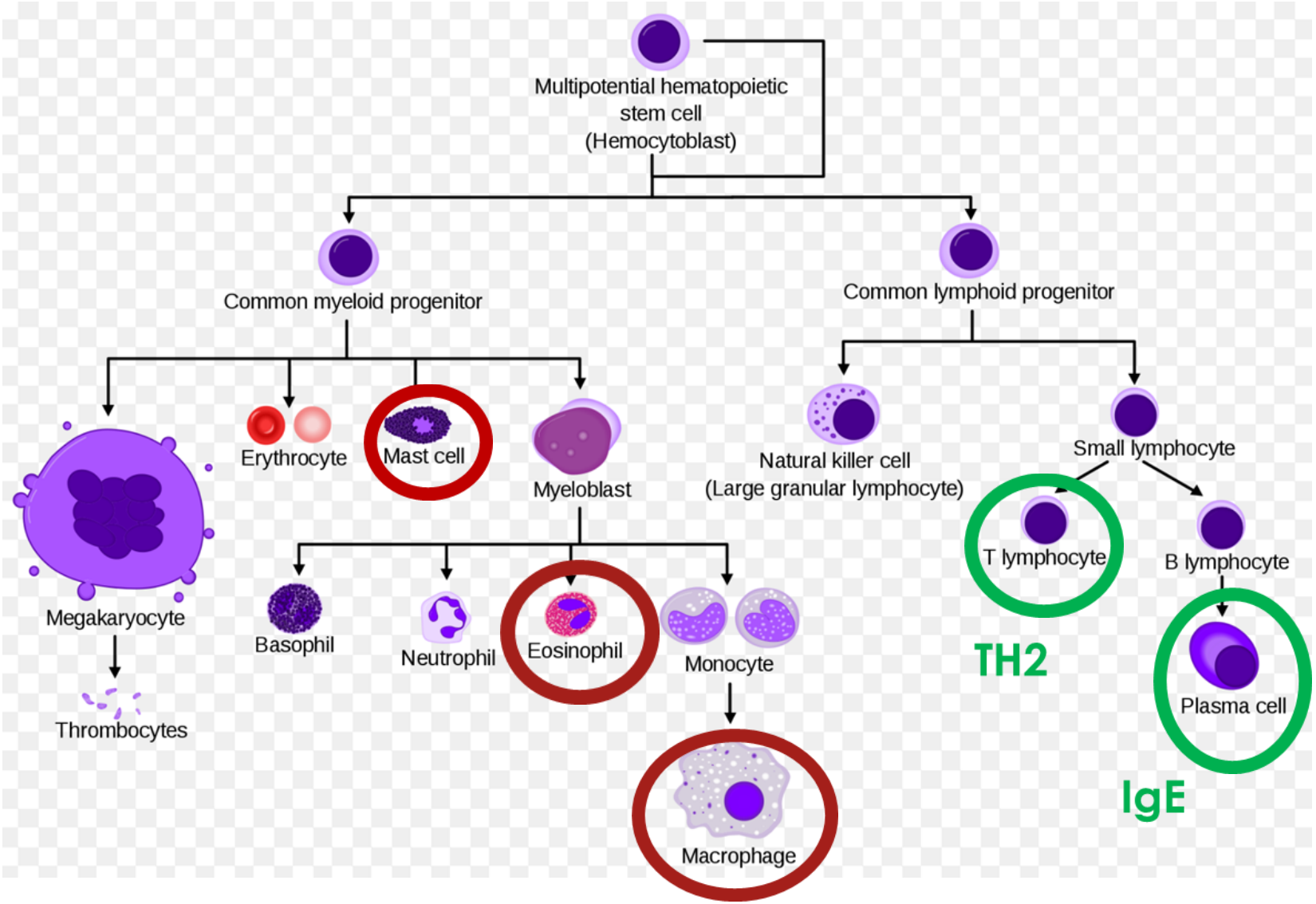
ALLERGIC	*NON-ALLERGIC*

• Atopic (extrinsic)
• Most common form
• Peak age 2nd decade
• Stronger family history
• IgE to specific antigens
  ◦ Dust, pollen, dander, mold
• Immunomodulators
	• Non-atopic (intrinsic)
	• Less common (10%)
	• Later age of onset
	• Greater inflammatory cell infiltrate
	• Triggers not allergy related
	  ◦ Exercise, cold/dry air, smoke, viruses, fumes, medications
	• Bronchial thermoplasty

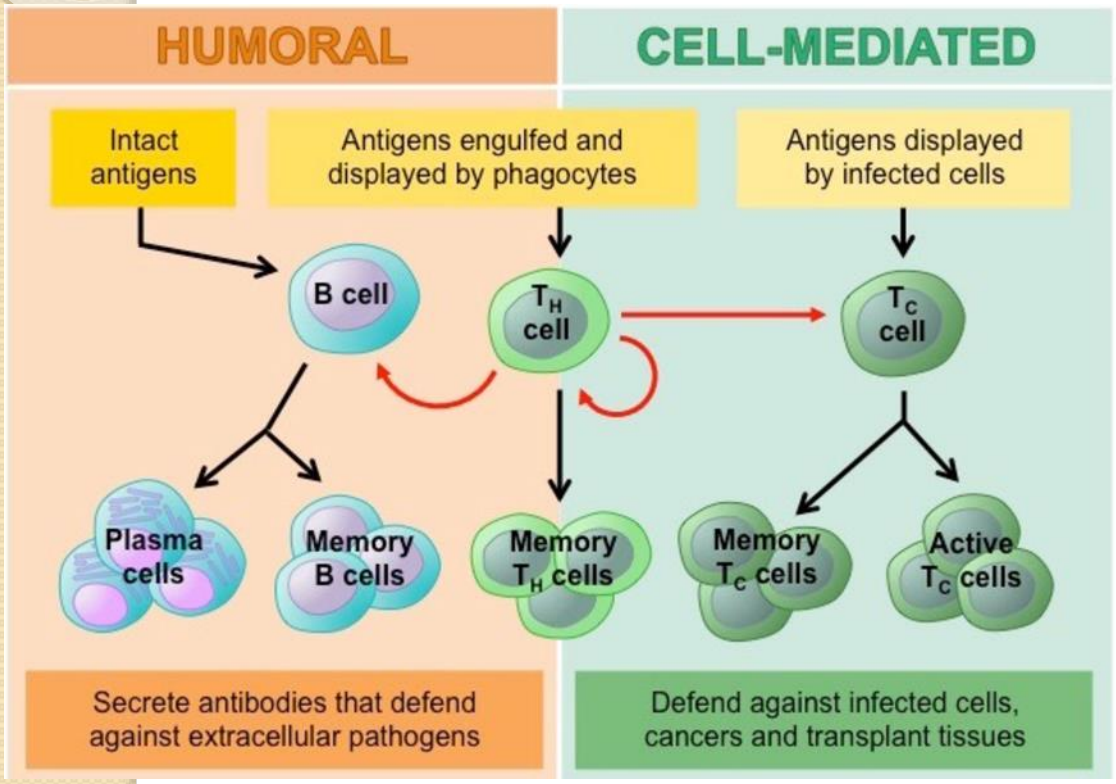
Innate immune system	*Adaptive immune system*
• Nonspecific defense mechanism when an antigen is presented: ◦ Physical barriers ◦ Chemicals in the blood ◦ Immune system cells	• Antigen specific immune response • More complex mechanism • Antigen must first be processed and recognized ◦ Cells that attack ◦ Memory cells

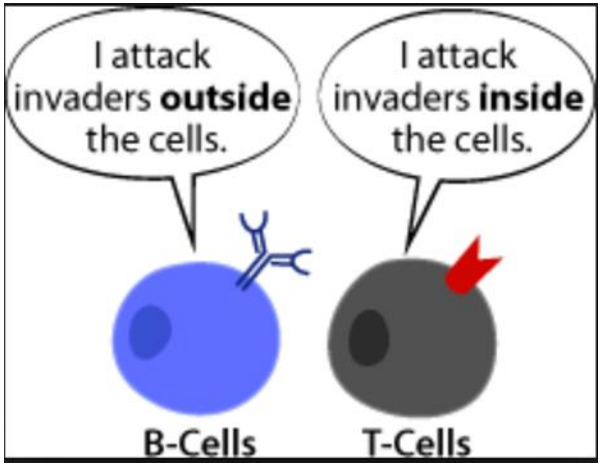
THESE DISTINCTIONS ARE NOT MUTUALLY EXCLUSIVE

Back to the Basics


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Megakaryocyte
Thrombocytes
Erythrocyte
Mast cell
Myeloblast
Basophil
Neutrophil
Eosinophil
Monocyte
Macrophage
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
T lymphocyte
TH2
B lymphocyte
Plasma cell
IgE

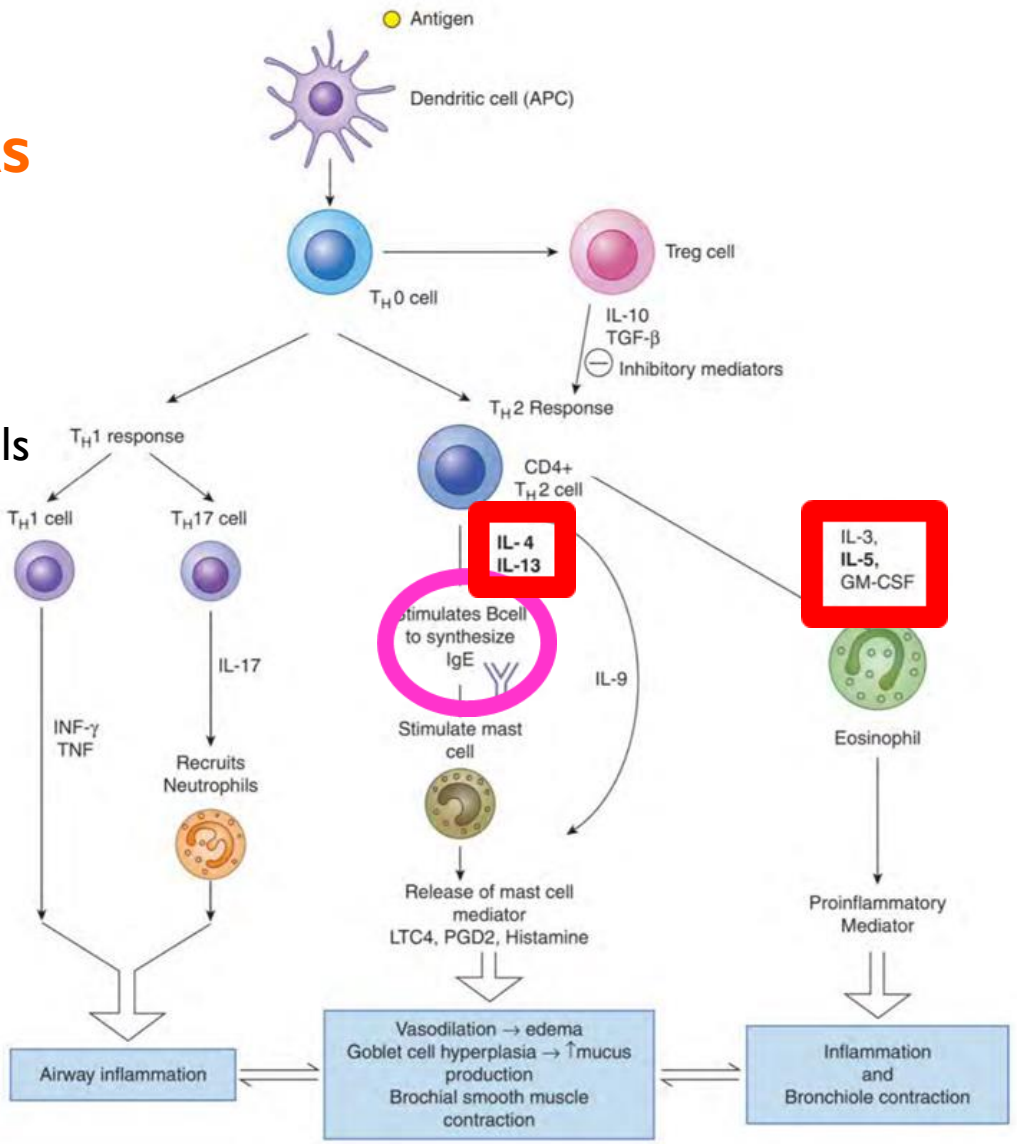
Adaptive Immune System



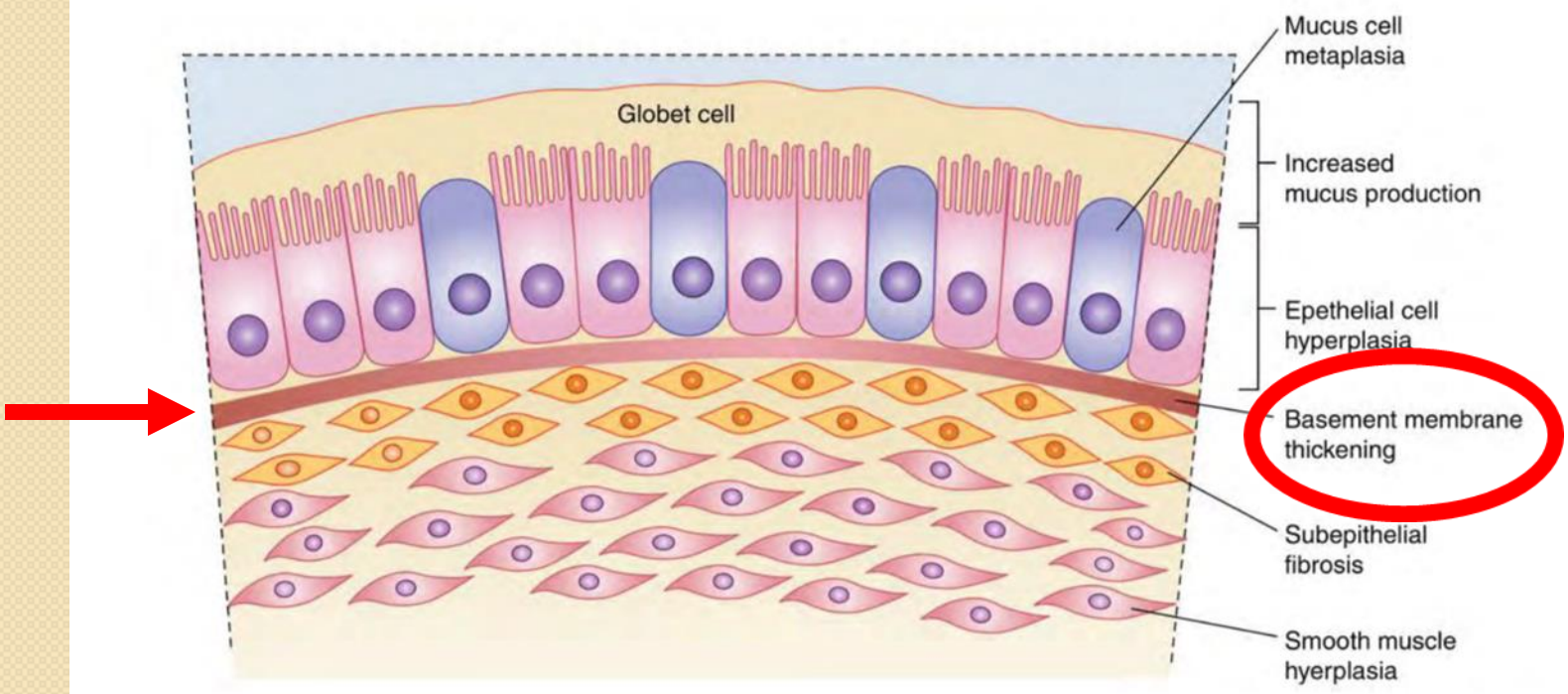


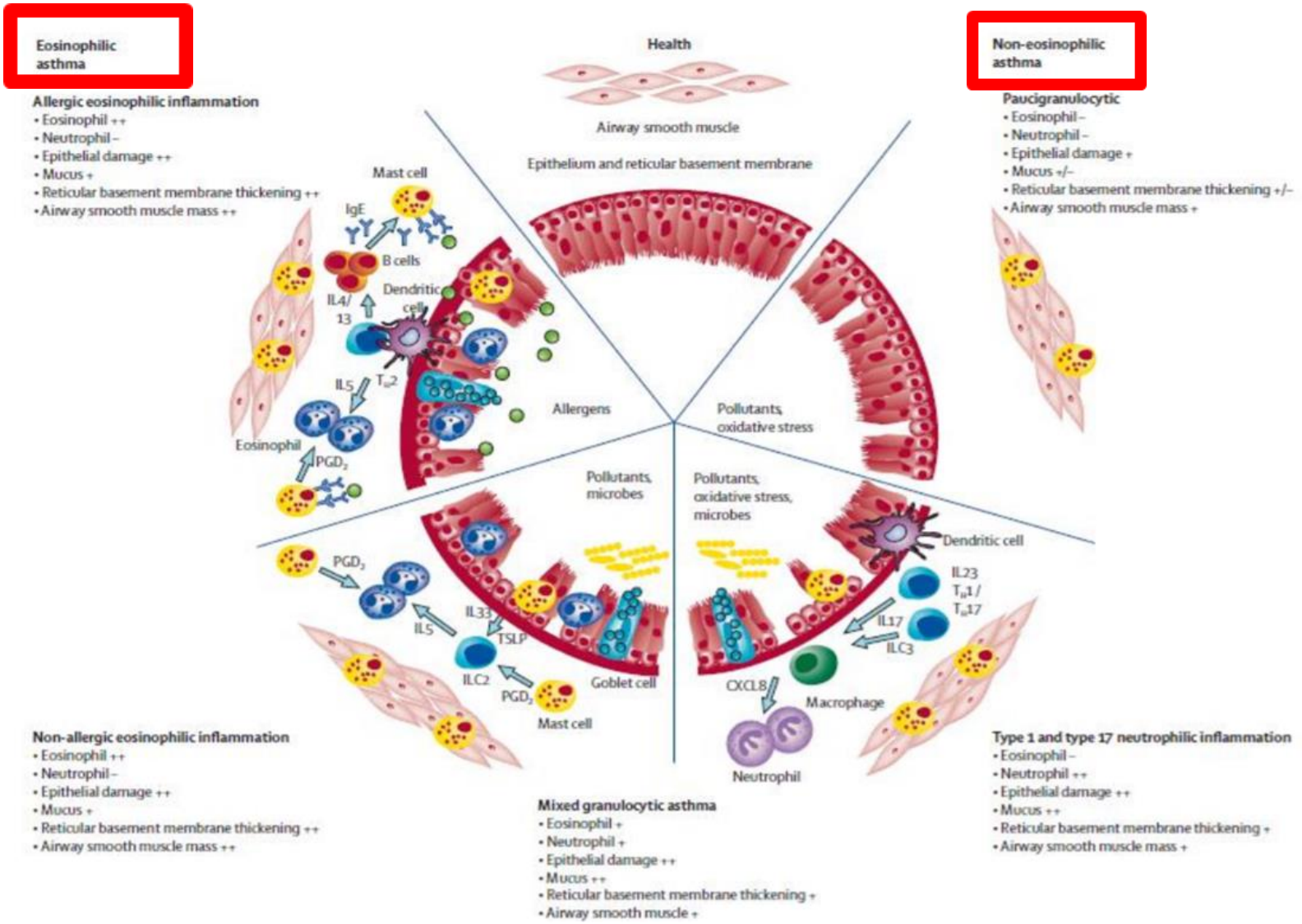
MAJOR CONTRIBUTORS

-TH2 LYMPHOCYTE
  IL5, IL4, IL13
  Promote IgE and eosinophils
- EOSINOPHIL
- MAST CELL
- NEUTROPHIL



ATS Pulmonary Board Review 2015


Globet cell
Mucus cell metaplasia
Increased mucus production
Epethelial cell hyperplasia
Basement membrane thickening
Subepithelial fibrosis
Smooth muscle hyerplasia



www.thelancet.com Dec 2017

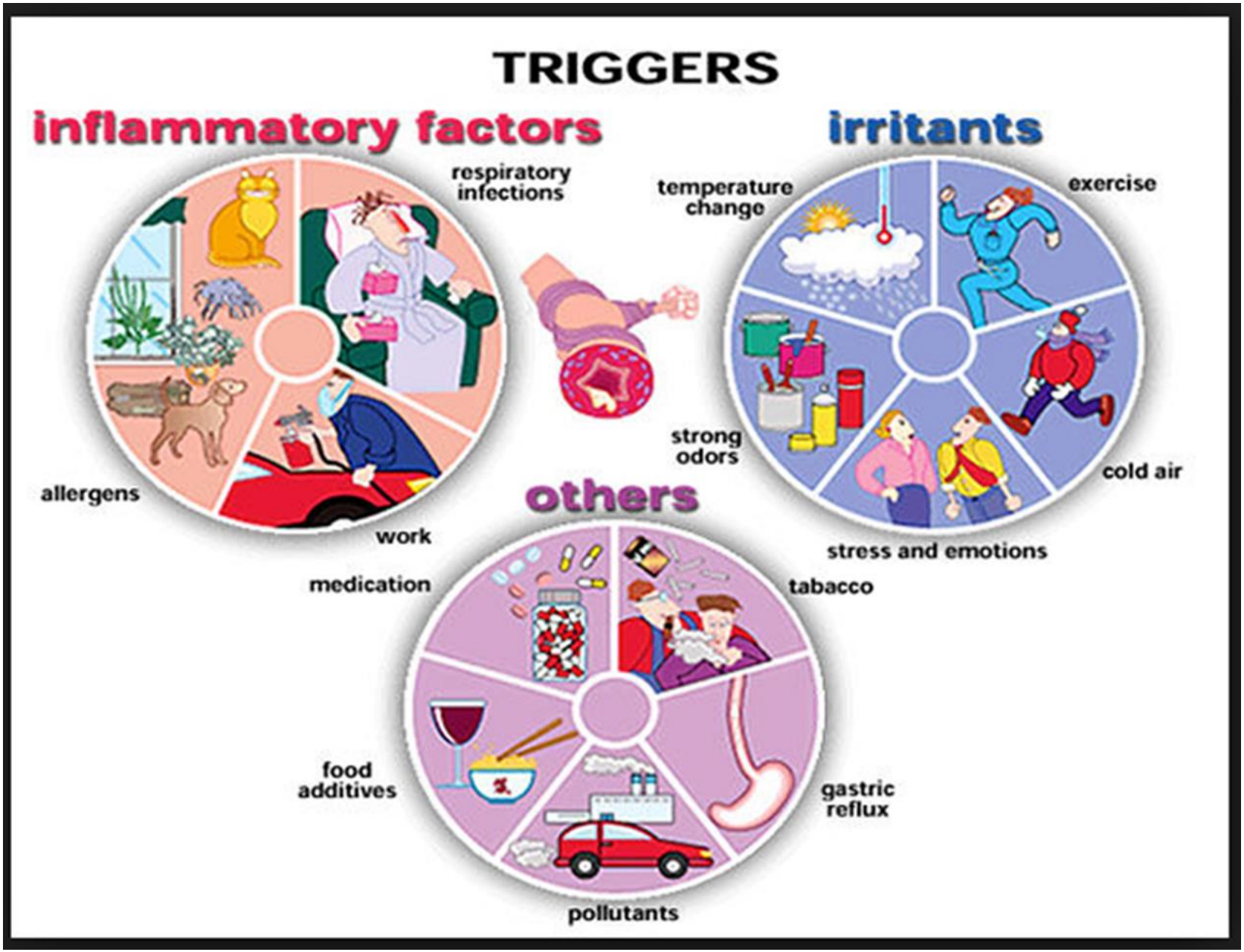
Inflammatory Mediators: COPD

Table 3-23. Overview of Asthma and COPD Pathogenesis

Feature	Asthma	COPD
Inciting factor	Allergen or irritant	Smoking or irritant
Major cell types	Epithelial cells, T_h2 cells (CD4+) Mast cells, eosinophils	T_h1 and T_C1 cells (CD8+) Neutrophils, macrophages
Mediators	IL-4, IL5, IL-13	LTB4, TNFα, IL-8
Airway and parenchymal involvement	Mainly large airway No parenchymal involvement	Small airway fibrosis Parenchymal destruction
Pathological changes	Subepithelial fibrosis Smooth muscle hyperplasia+++ Mucous metaplasia Basement membrane thickening	Peribronchial fibrosis Smooth muscle hyperplasia+ Mucous metaplasia Alveolar destruction
Airflow limitation	**Reversible** **Airflow limitation** **Partially reversible**	

ASTHMA DIAGNOSIS

- Pattern of symptoms + objective data + response to therapy
  - Nocturnal symptoms
  - Diurnal variation
- Spirometry
  - Airflow obstruction
    - FEV1/FVC, FEV1, PEF, TLC, DLCO
  - Reversibility
    - 12% or 200 cc increase
- CXR/CT chest
- Laboratory data
  - IgE, serum eosinophils
  - Allergy testing
- Bronchial hyperreactivity
  - Methacholine challenge testing
    - 20% decline in FEV1
    - Sensitive, not specific
- feNO
  - Levels are high (due to eosinophils)
  - Assessment, management, long term monitoring


TRIGGERS
inflammatory factors
respiratory infections
allergens
work
irritants
temperature change
exercise
strong odors
cold air
stress and emotions
others
medication
tabacco
food additives
gastric reflux
pollutants

Contributing Factors

- GERD
- Sinus disease
- OSA/Obesity
- Chronic aspiration
- Vocal Cord Dysfunction
  - Mid-chest tightness, dyspnea, dysphonia/stridor, partial response to asthma medication
  - Adduction of VC on laryngoscopy

Asthma Syndromes

- **Allergic Asthma**
  - Most common form of asthma in adults
  - Atopy, positive FH
- **Cough Variant**
- **Exercise Induced Bronchospasm**
  - Triggered by drying of airways
- **Occupational Asthma**
  - Farmers, factory workers, hairdressers
- **Aspirin Sensitive Asthma (Samter triad)**
  - Asthma, asa sensitivity, sinusitis/nasal polyposis
- **Reactive Airways Dysfunction Syndrome**
  - Exposure to high concentration of irritant; short lived
- **Virus-Induced bronchospasm**
- **Allergic Bronchopulmonary Aspergillosis**
  - Colonization of aspergillus sp
  - Mucus plugging, bronchiectasis, asthma, fleeting infiltrates

Asthma Treatment

- Shift in our approach
  - No longer based on severity
  - Based on treatment response/control
- Goals
  - Improve quality of life with less daytime/nighttime symptoms
  - Avoid exacerbations
  - Minimize side effects/cost, minimize use of rescue mediations
- Toolbox
  - Inhaled corticosteroids, bronchodilators, and anticholinergics
  - Oral agents: corticosteroids, LTRA
  - Immunomodulatory biologic therapy
  - Bronchial thermoplasty
  - Allergy immunotherapy
- Environmental control
- Monitoring (symptoms/lung function/action plan)
- Ongoing education/partnership

SEVERITY COMPONENTS	INTERMITTENT	PERSISTENT ASTHMA: daily medication		
		MILD	MODERATE	SEVERE
Symptoms	Less than once a week	More than twice per week but not daily	Daily	Throughout the day
Nocturnal Symptoms	Less than twice a day per month	Three-four times per month	More than once a week but not every night	Often every night per week
Interference with activity	Brief exacerbations	Exacerbations may cause minor limitation of activity and sleep	Exacerbations more than twice a week and may cause some limitation of activity and sleep	Frequent exacerbations with marked limitation of physical activity
SABA use	≤ 2 days per week	>2 days per week, but not daily and not more than once on any day	Daily	Several times per day
Pulmonary Function Test	• Normal FEV_1 between exacerbations • FEV_1: >80% predicted • FEV_1/FVC: normal	• FEV_1: >80% predicted • FEV_1/FVC: normal	• FEV_1: >60% but <80% predicted • FEV_1/FVC: reduced 5%	• FEV_1: <60% predicted • FEV_1/FVC: reduced 5%
Recommended Treatment Strategy	**STEP- 1** *Preferred:* SABA PRN	**STEP- 2** *Preferred:* Low-dose ICS *Alternative:* Cromolyn, LTRA, Nedocromil, or Theophylline	**STEP- 3** *Preferred:* Low-dose ICS + LABA *OR* Medium-dose ICS *Alternative:* Low-dose ICS + either LTRA, Theophilline, or Zileuton Consider Oral Steroids	**STEP- 4 or 5** STEP- 4 : Preferred: Medium-dose ICS + LABA Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton STEP- 5 : Preferred: High-dose ICS + LABA AND Consider Omalizumab for patients who have allergies Consider Oral Steroids

Step-up if needed (First, check adherence, environmental control, and comorbid conditions)

ASSESS CONTROL

Step down if possible (and asthma is well controlled atleast 3 months)

Each Step: patient education, environmental control, and management of comorbidities.
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

Quick-relief medication for all patients:
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIA) generally indicates inadequate control and the need to step up therapy.

Adopted from National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08-4051, 2007.

Levels of Asthma Control
(Assess patient impairment)

Characteristic	Controlled (All of the following)	Partly controlled (Any present in any week)	Uncontrolled
Daytime symptoms	Twice or less per week	More than twice per week	3 or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms / awakening	None	Any	
Need for rescue / "reliever" treatment	Twice or less per week	More than twice per week	
Lung function (PEF or FEV_1)	Normal	< 80% predicted or personal best (if known) on any day	

Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side effects)

Traditional Pharmacologic Asthma Treatment

- Direct bronchodilators (short/long)
  - B2 agonists (increases cAMP)
    - Albuterol, levalbuterol
    - Salmeterol, vilanterol
  - Anti-cholinergics (M3 receptor)
    - Ipratropium bromide
    - Tiotropium, glycopyyronium, umeclidium, aclidinium
  - Methylxanthines
    - Aminophylline, theophylline
  - Adrenergic agonists
    - Epinephrine
- Anti-inflammatory medications
  - Corticosteroids (inhaled, PO, IV, IM)
    - Fluticasone, beclomethasone
    - Prednisone
- Mast cell stabilizers (inhibits histamine and tryptase)
  - Cromolyn sodium
  - Nedocromil (not for acute attacks)
- Leukotriene antagonists
  - 5 lipoxygenase synthesis inhibitor
    - zileuton
  - Leukotriene receptor antagonist
    - montelukast

Traditional Pharmacologic Asthma Treatment

- Benefits of LABA
  - Improve lung function/symptoms
  - Decrease in exacerbations when used with ICS
- **DO NOT USE LABA WITHOUT ICS**
- ICS/LABA superior to higher dose ICS
- Step down therapy once control achieved
- Inform patients of concerns seen in asthma

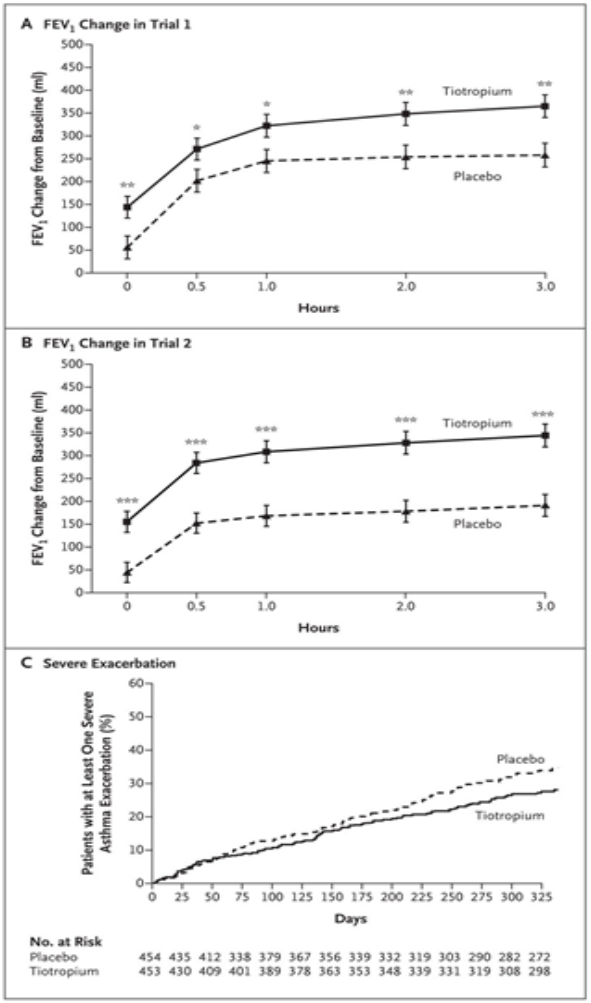
- SMART Trial
  - Double blind, randomized observational trial 28 wk in 26K pts
  - Salmeterol v placebo added to "usual care"
  - Salmeterol was associated with greater asthma related deaths and life threatening exacerbations in AA population (no difference in Caucasian)

Long-Acting Beta agonists (LABAs) and Inhaled Corticosteroids (ICS): Drug Safety Communication - Boxed Warning About Asthma-Related Death Removed

Greening. Lancet. 1994; Bateman AJRCCM. 2004; Pauwels, NEJM. 1997. Nelson. Chest. 2006. FDA 2017

LAMA for the Treatment of Uncontrolled Asthma

- 2 replicate, randomized controlled study 912 patients
- Inclusion criteria
  - FEV1<80%, Mean FEV1 62%
  - >1 severe exacerbation in prior year
  - Mean age 53
- Add on tiotropium or placebo
- Result
  - Tiotropium associated with
    - Longer time to first exacerbation
    - More sustained bronchodilation



Kerstjens, HAM. NEJM. 2012(367):1198-1207

Chest. 2015 Feb;147(2):388-396. doi: 10.1378/chest.14-1698.

What is the role of tiotropium in asthma?: a systematic review with meta-analysis.

Rodrigo GJ[1], Castro-Rodríguez JA[2].

Author information

Add on to ICS or add on to ICS/LABA:
Increased PEF and FEV1, decreased rate of exacerbations, improved asthma control
Not inferior to salmeterol

Abstract

BACKGROUND: The role of tiotropium for the treatment of asthma has not yet been clearly defined. The aim of this systematic review was to assess the efficacy and safety of tiotropium in patients with asthma.

METHODS: Randomized placebo-controlled trials were included. Primary outcomes were peak and trough FEV1 and morning and evening peak expiratory flow (PEF).

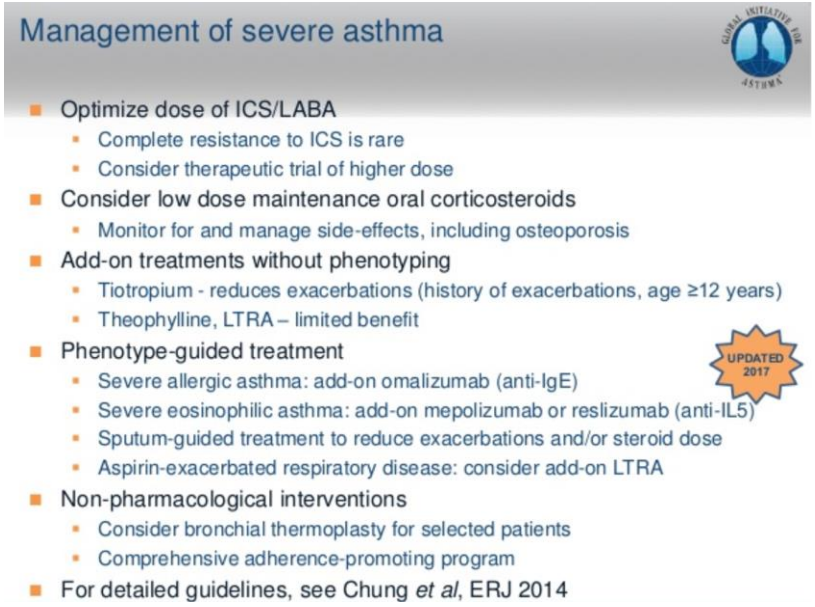
RESULTS: Thirteen studies (4,966 patients) were included. Three different therapeutic protocols were identified. Tiotropium as an add-on to inhaled corticosteroids (ICSs) showed statistically and clinically significant increases in PEF (22-24 L/min) and FEV1 (140-150 mL). Additionally, tiotropium decreased the rate of exacerbations (number needed to treat for benefit [NNTB], 36) and improved asthma control. The use of tiotropium in patients poorly controlled despite the use of medium to high doses of ICS was not inferior to salmeterol. Finally, the use of tiotropium as an add-on to ICS/salmeterol combination increased pulmonary function to a clinically significant magnitude, reduced asthma exacerbations (relative risk, 0.70; 95% CI, 0.53-0.94; $P < .02$; $I2 = 0\%$; NNTB, 17), and improved asthma control compared with ICS/salmeterol. Tiotropium was well tolerated, and no potential safety signals were observed.

CONCLUSIONS: Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/salmeterol. Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations.

Many studies have demonstrated the efficacy of LAMA add on therapy irrespective of allergic or inflammatory components

Asthma Treatment: LAMA Changing Paradigm

- Tiotropium FDA approved (asthma)
  - adults 2015
  - children (>6y) 2017
- Can be used as add on therapy
  - ICS/LABA + LAMA
  - ICS/LAMA
- Ongoing research
  - LAMA monotherapy??



ginasthma.org

Table 2

Asthma Management Therapies

Class	Examples	Properties and Uses
SABAs	Albuterol, levalbuterol	Relax airway smooth muscle; treatment of choice for acute symptoms
LABAs	Salmeterol, formoterol	Bronchodilation lasting for ≥ 12 hours; usually used in combination with ICS after step 2
ICS	Beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone	Reduce airway hyperresponsiveness, decrease inflammatory cell migration and activation, block late-phase reactions to allergens
OCS	Prednisone	Systemic anti-inflammatory effects; used for moderate to severe exacerbations to accelerate recovery and prevent late-phase response; may be used for long-term control
Mast cell stabilizers	Cromolyn sodium, nedocromil	Interfere with release of inflammatory mediators from mast cells; maintenance therapy for mild to moderate asthma or as prophylaxis for exercise-induced asthma
Leukotriene modifiers	Montelukast, zafirlukast, zileuton	Interfere with leukotriene mediators released from mast cells, eosinophils and basophils; prophylaxis of exercise-induced asthma and long-term treatment as alternative to low doses of ICS
Methylxanthines	Theophylline, aminophylline	Mild to moderate bronchodilation; toxic at higher doses
Anticholinergics	Ipratropium bromide	Enhance effects of SABAs in acute attacks by inhibiting muscarinic cholinergic receptors and reducing vagal tone of airway
Immunomodulators	Omalizumab	Binds to IgE, forming complexes that prevent initiation of allergic cascade by inhibiting mast cell and basophil degranulation; reserved as add-on therapy for patients ≥ 12 years with refractory asthma (steps 5 and 6)

Abbreviations: ICS, inhaled corticosteroids; LABAs, long-acting beta-agonists; OCS, oral corticosteroids; SABAs, short-acting beta-agonists

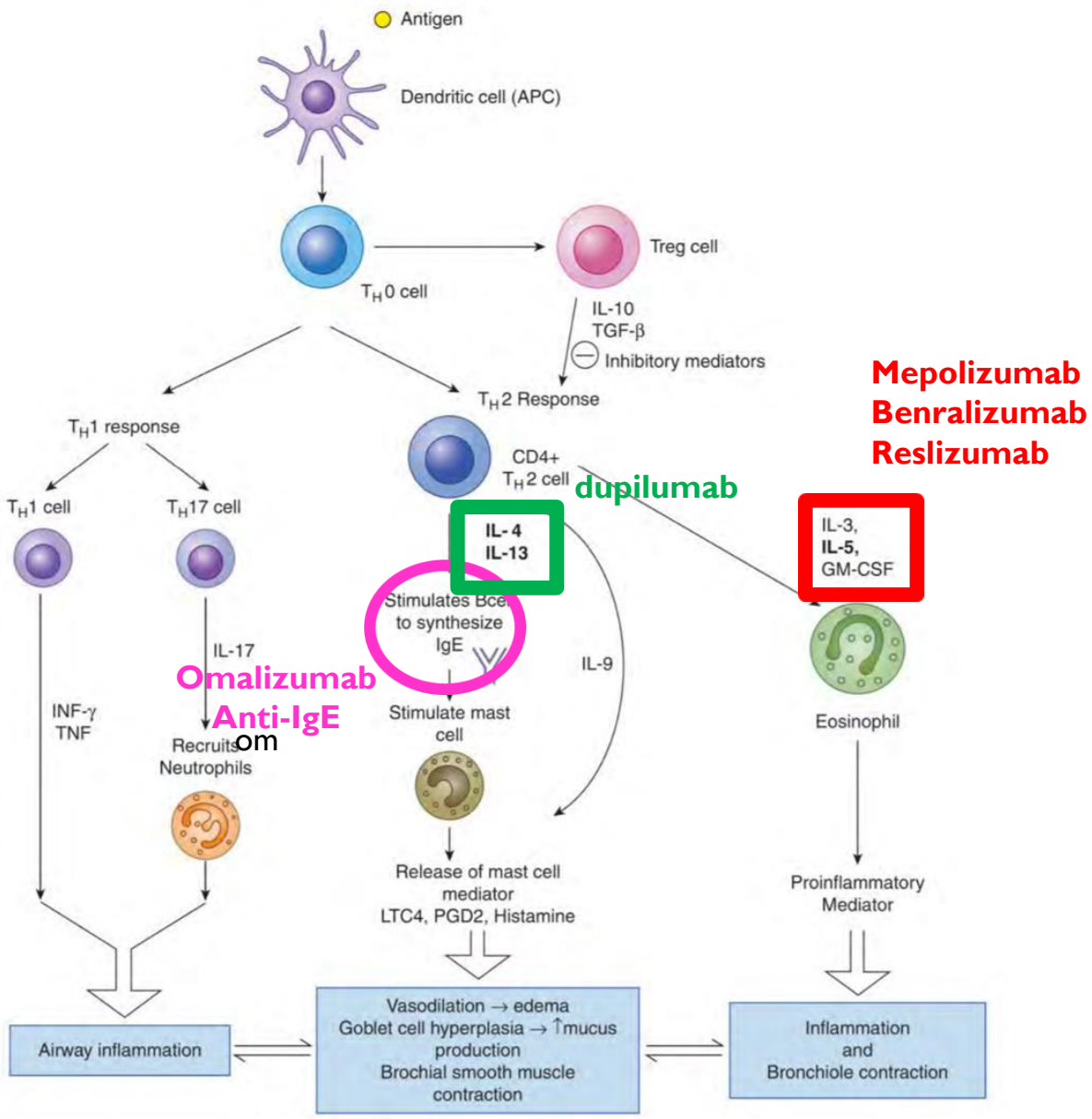
Adapted from: National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. *Bethesda, MD: National Heart, Lung, and Blood Institute, US Dept of Health and Human Services; 2007. NIH publication 08-5846.*

Immunomodulators

- Anti-IgE
  - omalizumab
- Anti-IL5
  - Mepolizumab
  - Benralizumab
  - Reslizumab
- Anti-IL4 and IL13
  - Dupilumab
- New on the horizon
  - Anti-IL5, IL4, and IL13

- When do you use them?
  - Moderate to severe allergic asthma
  - Refractory to traditional therapy
- What do they do?
  - Decrease exacerbations
  - Decrease steroid use
  - Improve lung function
  - Improve QOL

Correns J. NEJM. 2011. 365(12):1088.
Wenzel S. NEJM 2013. 368: 2455-2466.
Pavord ID. Lancet 2012. 380: 651-659



ATS Pulmonary Board Review 2015

Anti-IgE: Omalizumab

- Indication
  - Moderate/severe persistent allergic asthma
  - High IgE, +/- high eosinophil
  - Positive allergy skin testing
- Dosing
  - Based on IgE level and weight/subcutaneous injection; frequent dosing
  - Approved for adults and children >12y (2003), age >6y (2016)
  - Don't need to follow IgE levels
- Data
  - Moderate/severe asthma: decreased exacerbations, decreased steroid dosing
  - Severe asthma: conflicting results but improved QOL
- Caution
  - Monitor patients after administration: Anaphylaxis rare
  - Slight increase in risk of malignancy (<1%), cardio and cerebrovascular disease, parasitic infections
- Cost
  - $12,000/y v $2500/y ICS/LABA

Busse, JACI. 2001; Holgate, Clin Exp All. 2004; Humbert, Allergy. 2005; www.fda.gov

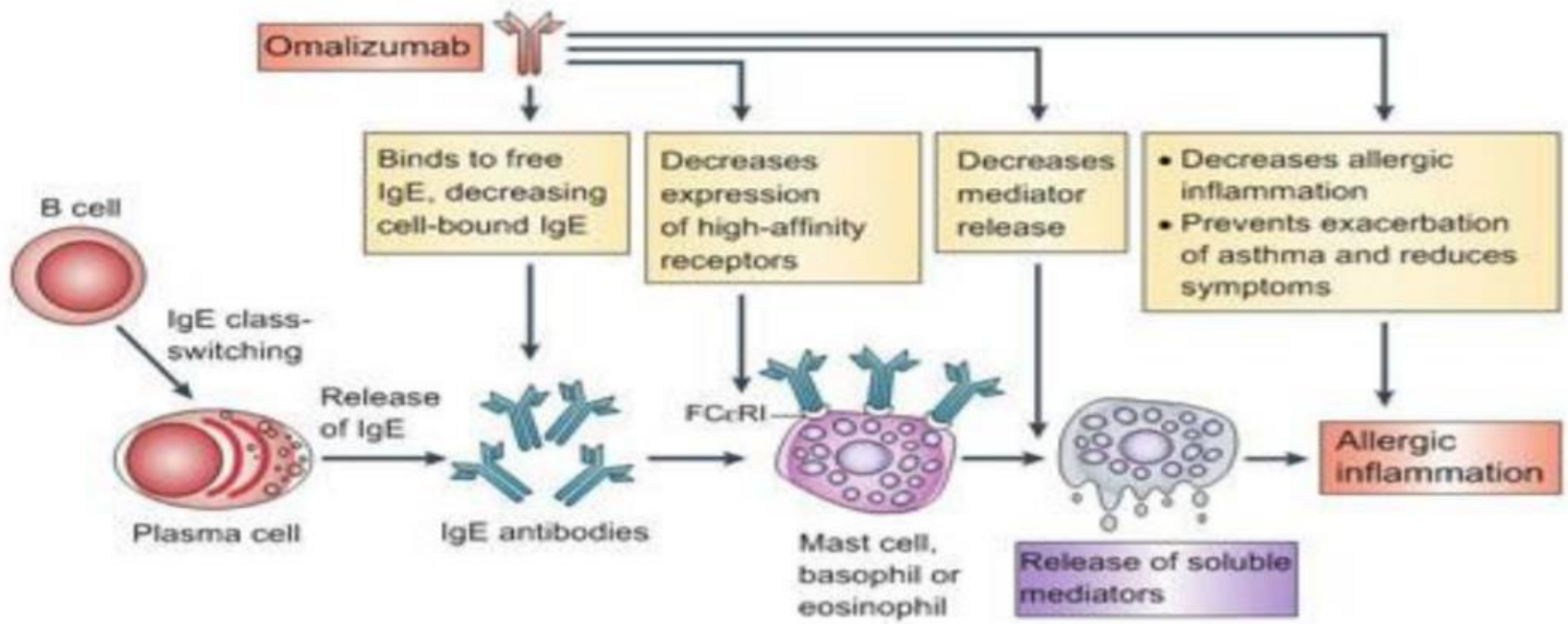
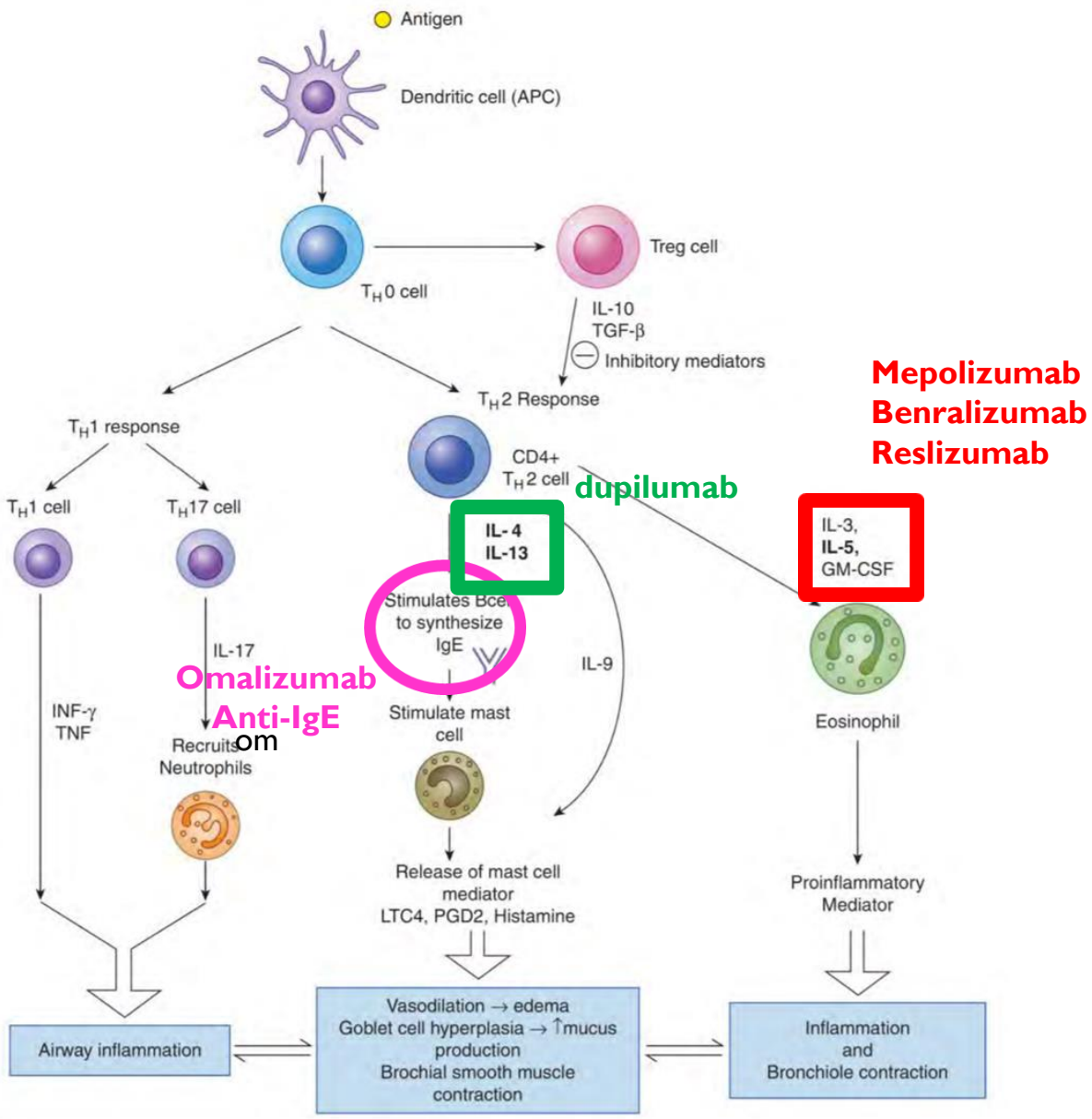


Figure 1. Mechanisms of action of omalizumab in allergic asthma.
Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Immunol,[14] copyright 2008.
Abbreviation: Fc RI, high-affinity IgE receptor.

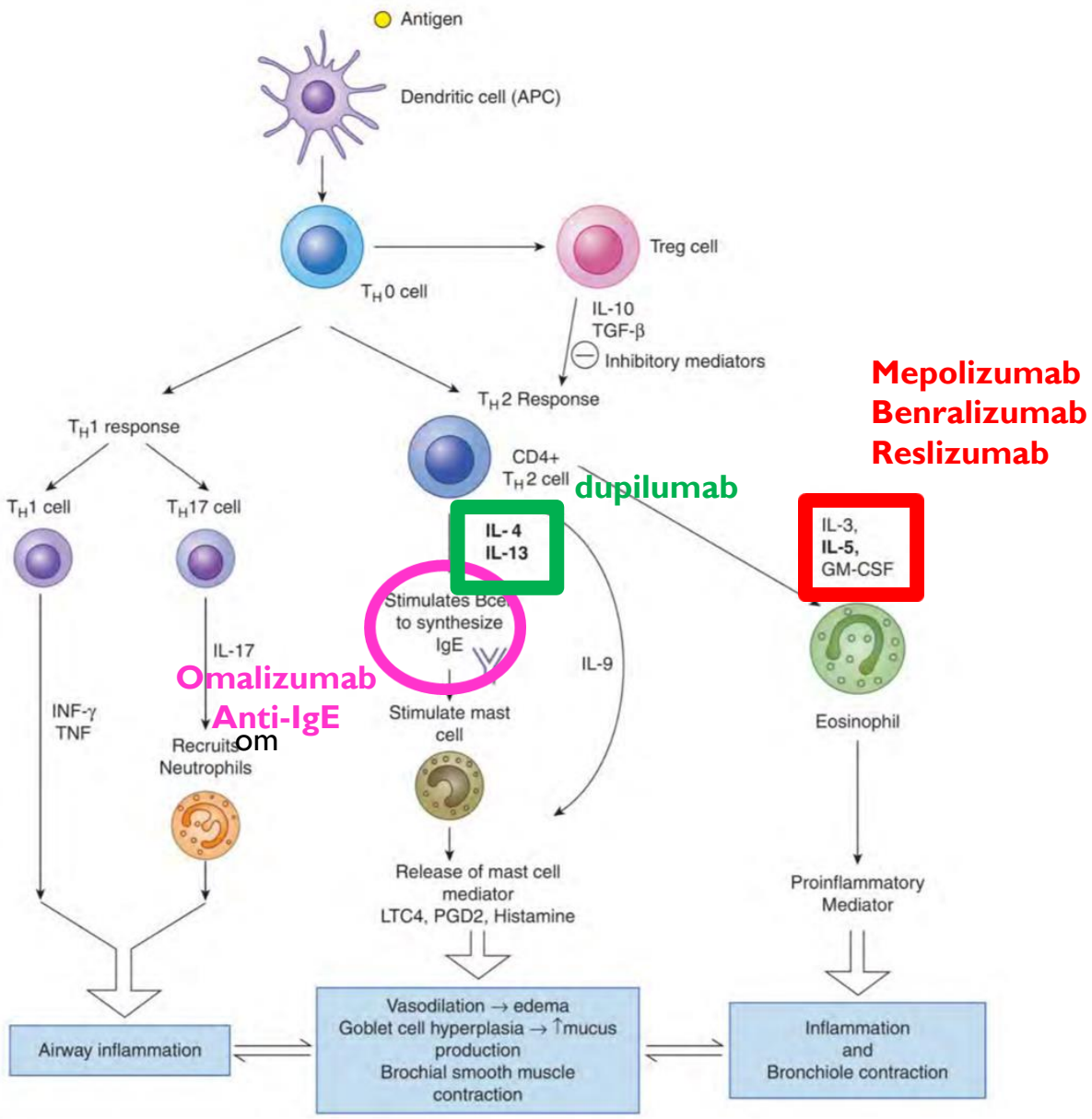


ATS Pulmonary Board Review 2015

Anti-IL5: Mepolizumab, Benralizumab, Reslizumab

- Indication
  - Severe allergic asthma with eosinophilia refractory to traditional therapy
- Dosing
  - Monoclonal antibody binds and inactivates IL-5
  - Mepolizumab: fixed dose 100 mg, subcut, q4wk
  - Benralizumab: fixed dose 30 mg, subcut, q8wk
  - Reslizumab: weight based 3 mg/kg, IV, q4wk
- Caution
  - Risk of opportunistic infection: herpes zoster
  - Monitor patients after administration: Anaphylaxis rare
  - Pregnancy category not assigned
- Cost
  - $35,000 annually/$1000 per vial reslizumab

www.fda.gov; www.drugs.com



ATS Pulmonary Board Review 2015

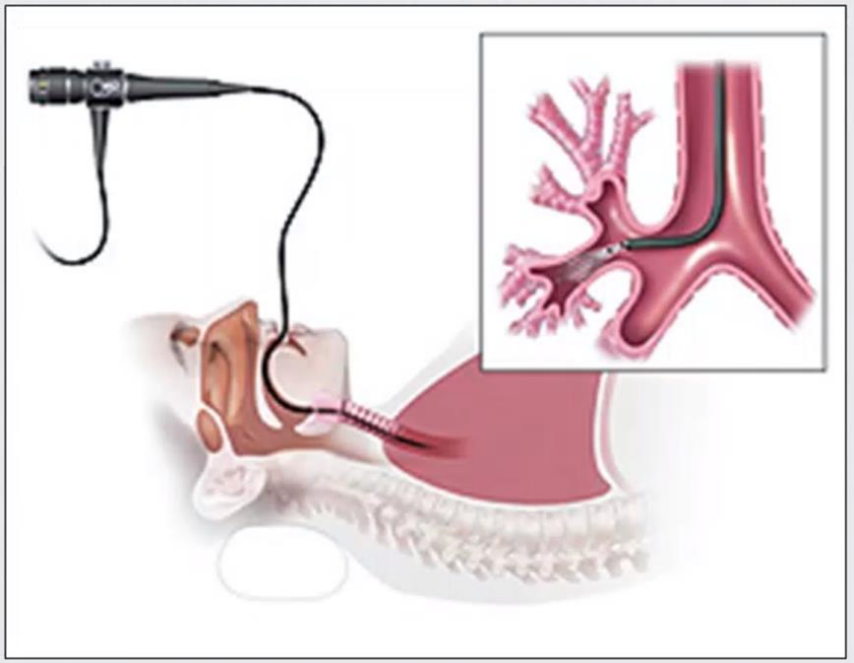
Anti-IL4 and IL13: Dupilumab

- Indication
  - Moderate/severe allergic asthma, atopy, eosinophilia
- FDA approval
  - Atopic dermatitis: March 2017
  - Asthma: Now approved 2018!!
- Data
  - QUEST and VENTURE trials
  - LIBERTY ASTHMA PROGRAM
- Cost
  - $38,000 annually
- Biggest advantage
  - AT HOME ADMINISTRATION

www.clinicaltrials.gov; www.fda.gov. Castro M et al. NEJM 2018. 378: 2486-96. Rabe KF. NEJM. 2018. 378: 2475-85.

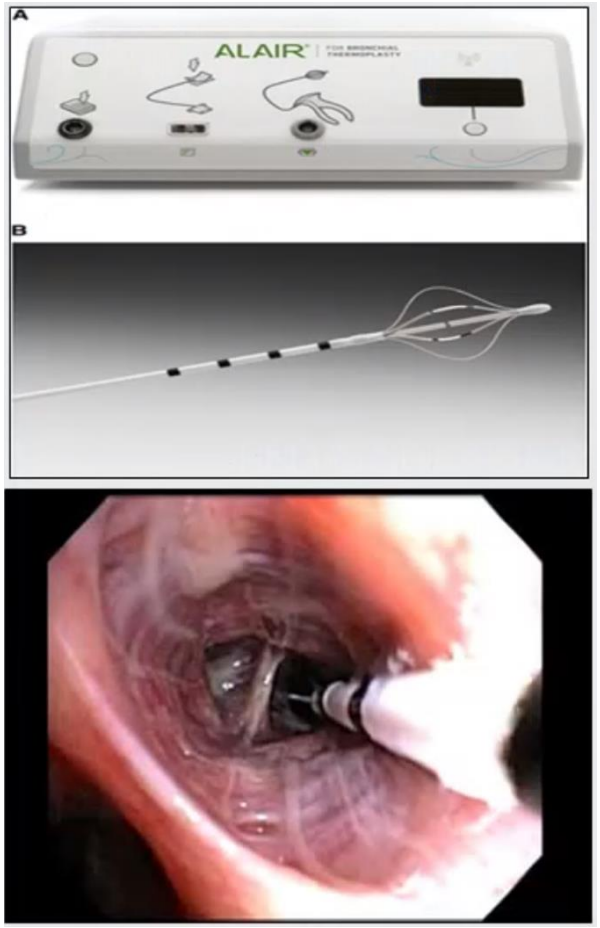
Bronchial thermoplasty

- FDA approved 2010
- Nonpharmacologic therapy for adults with severe asthma refractory to available medical therapy
- Catheter delivered radio frequency energy which heat the lining of the lung to 65C
- Targets airway remodeling by reducing airway smooth muscle mass which is responsible for
  - Bronchoconstriction
  - Mucus hypersecretion
  - Airway hyperresponsiveness



Chupp G. ERJ 2017 Aug;
Castro AJRCCM 2010;
Wechler ME. J Allergy Clin Immunol 2013 (132)

- Repeated procedures several weeks apart targeting different lobes
- Benefit data
  - 40% reduction in asthma exac
  - 80% reduction in ER visits
  - 65% reduction days lost work/school
  - 70% reduction in hospitalizations
- Risks
  - Bronchospasm following procedure
  - Hemoptysis, atelectasis, infection
  - Avoid with pacemaker/AICD
  - Avoid FEV1<65%



Chupp G. ERJ 2017 Aug;
Castro AJRCCM 2010;
Wechler ME. J Allergy Clin Immunol 2013 (132)

Also important to review…

- Alpha 1 Antitrypsin deficiency
- Cystic Fibrosis
- Bronchiectasis
  - Right Middle Lobe Syndrome
  - Ciliary Dyskinesia Syndrome
  - Allergic Bronchopulmonary Aspergillosis


COPD
CLINIC