ASTHMA AND COPD
SIMILARITIES AND DIFFERENCES

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Marc Peters -Golden, MD

The Overlap Between Asthma and COPD

COPD=chronic obstructive pulmonary disease.

Adapted from American Thoracic Society. *Am J Respir Crit Care Med.* 1995;152(5 pt 2):S77-S121.
Soriano JB, et al. *Chest.* 2003;124:474-481.
Jeffery PK. *Am J Respir Crit Care Med.* 2001;152:S28-S38.

The Dutch Hypothesis

- **Various forms of airway obstruction are different expressions of a single disease**
  - Chronic nonspecific lung disease (CNSLD)
- **Host and environmental factors play a role in pathogenesis**
  - Host factors: atopy and AHR
    - Other endogenous factors: sex and age
  - Exogenous factors: allergens, viral infections, smoking (pollutants)
- **Diffuse airway obstruction = common pathophysiologic characteristic**

Orie et al. Bronchitis II Second International Symposium. Assen, Netherlands: Royal Van Gorcum; 1964:398-99

The British Hypothesis

- **Asthma and COPD are distinct entities caused by different mechanisms**
  - Differences in inflammation
  - Airway remodeling vs alveolar remodeling
  - Epidemiology

Outline:
Are There Relationships Between Asthma and COPD?

- Definitions
- Impact
- Risk factors
- Pathophysiology
- Pulmonary function and disease progression
- Clinical presentation
- Treatment strategies

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What Is Asthma? What Is COPD?

Asthma[1]

- A **chronic inflammatory disorder** of the airways in which many cells and factors play a role
- Inflammation results in
  - **Recurrent symptoms**
  - Variable **airflow obstruction** that is mostly **reversible**
  - Increase in existing **bronchial hyperresponsiveness**

COPD[2]

- A **preventable and treatable** disease
- Associated with significant **extrapulmonary effects** and important **comorbid conditions**
- Characterized by airflow limitation that is
  - **Not fully reversible**
  - **Usually progressive**
  - Associated with an **abnormal inflammatory response** to noxious particles or gases

1. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed August 29, 2007.
2. Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989. Accessed November 21, 2008.

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The Burden of Asthma

- Asthma is one of the most common chronic diseases worldwide with an estimated 300 million affected individuals.
- Prevalence increasing in many countries; estimated that there may be an additional 100 million persons with asthma by 2025.
- Each year 180,000 deaths worldwide are attributable to asthma; many of the deaths are preventable, being due to suboptimal long-term medical care and delay in obtaining help during the final attack.
- A major cause of school/work absence
- Health care expenditures very high; developed economies might expect to spend 1-2 percent of total health care expenditures on asthma. Developing economies likely to face increased demand

COPD: Global Burden

- An estimated 210 million people worldwide have COPD
- COPD is a leading cause of morbidity and mortality worldwide.
- COPD ranks 12th as a burden of disease; by 2020 it is projected to rank 5th.
- More than 3 million people died of COPD in 2005; this represented 5% of all deaths worldwide
- Total deaths from COPD are projected to increase by >30% over the next 10 years without interventions to decrease risk, particularly exposure to tobacco smoke
- COPD will become the third-leading cause of death worldwide by 2030

World Health Organization. 2009.

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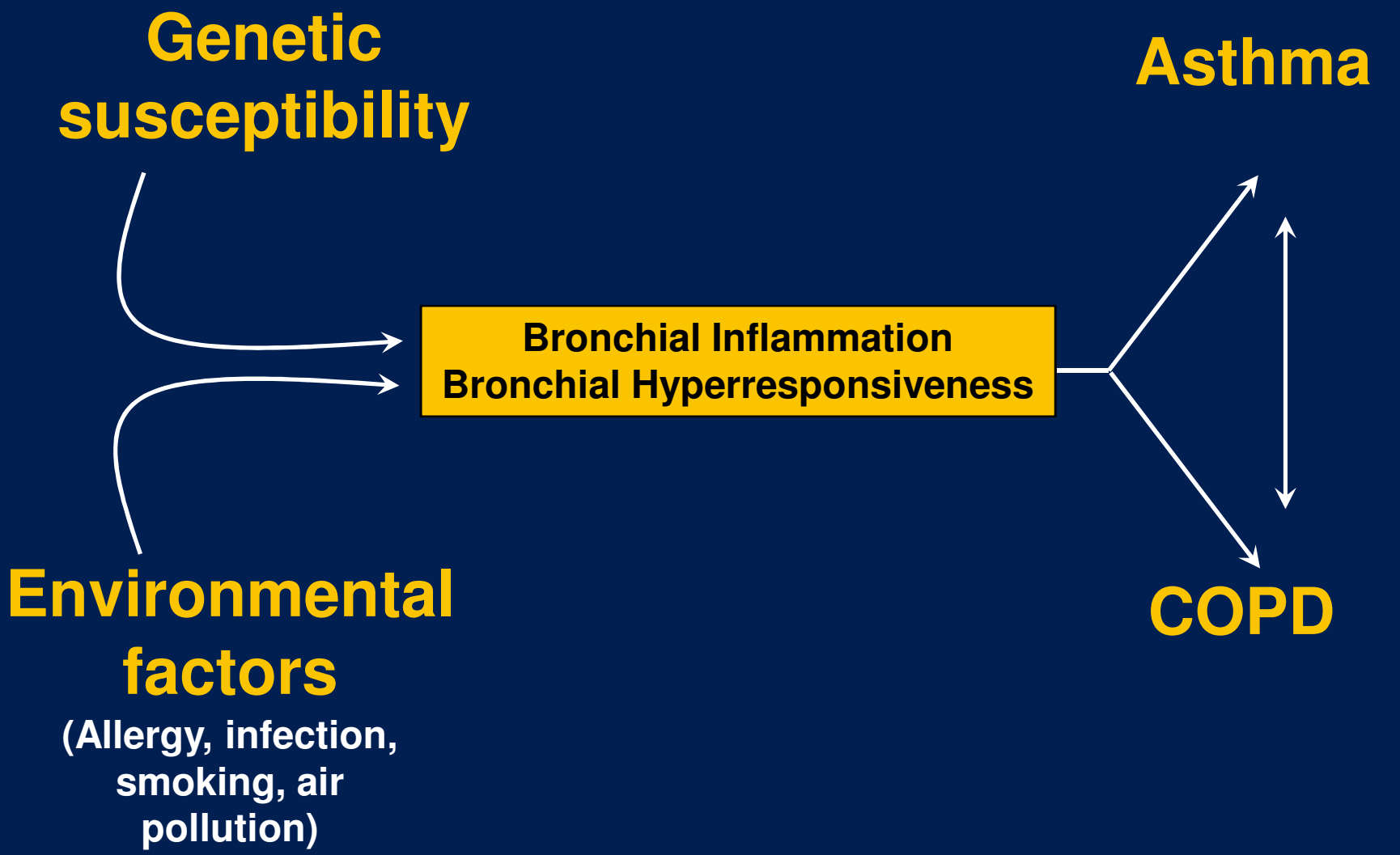
Interactions Between Asthma and COPD



Genetic Associations that Suggest a Common Origin in COPD & Asthma

- IgE
- BHR
- Rate of FEV1 decline
- Airway thickness

IL-13

ADAM33

van der Pouw Kraan TC. Genes Immun 1999;61–65 Howard TD. Am J Respir Cell Mol Biol 2001;377–384 van der Pouw Kraan TC. Genes Immun 2002;436–439 Ohar JA [abstract]. Eur Respir J 2001;P3588 Simpson A. Am J Resp Crit Care Med 2005;55-60 Holgate ST. Thorax 2005;466-69 van Diemen CC. Am J Resp Crit Care Med 2005;329-33 Jongepier H. Clin Exp Allergy 2004;757-60

Precipitating Factors for Asthma and COPD: Similarities and Differences

Asthma

- Genetic susceptibility
- Airway hyperresponsiveness
- Environmental
  - Allergen exposures
  - Viral respiratory infections
  - Tobacco smoke and air pollution
- Disease triggers
  - Exercise
  - Changes in weather
  - Exposure to cold air
  - Emotional factors
- Endocrine factors

COPD

- Host factors
  - α1-Antitrypsin deficiency
  - Other genetic factors (?) not yet identified
  - Airway hyperresponsiveness
  - Lung growth: reduced maximal attained pulmonary function
- Environmental factors
  - Tobacco smoke
  - Occupational dusts and chemicals
  - Outdoor and indoor air pollution
  - Infections: history of severe respiratory infection in childhood
  - Socioeconomic factors

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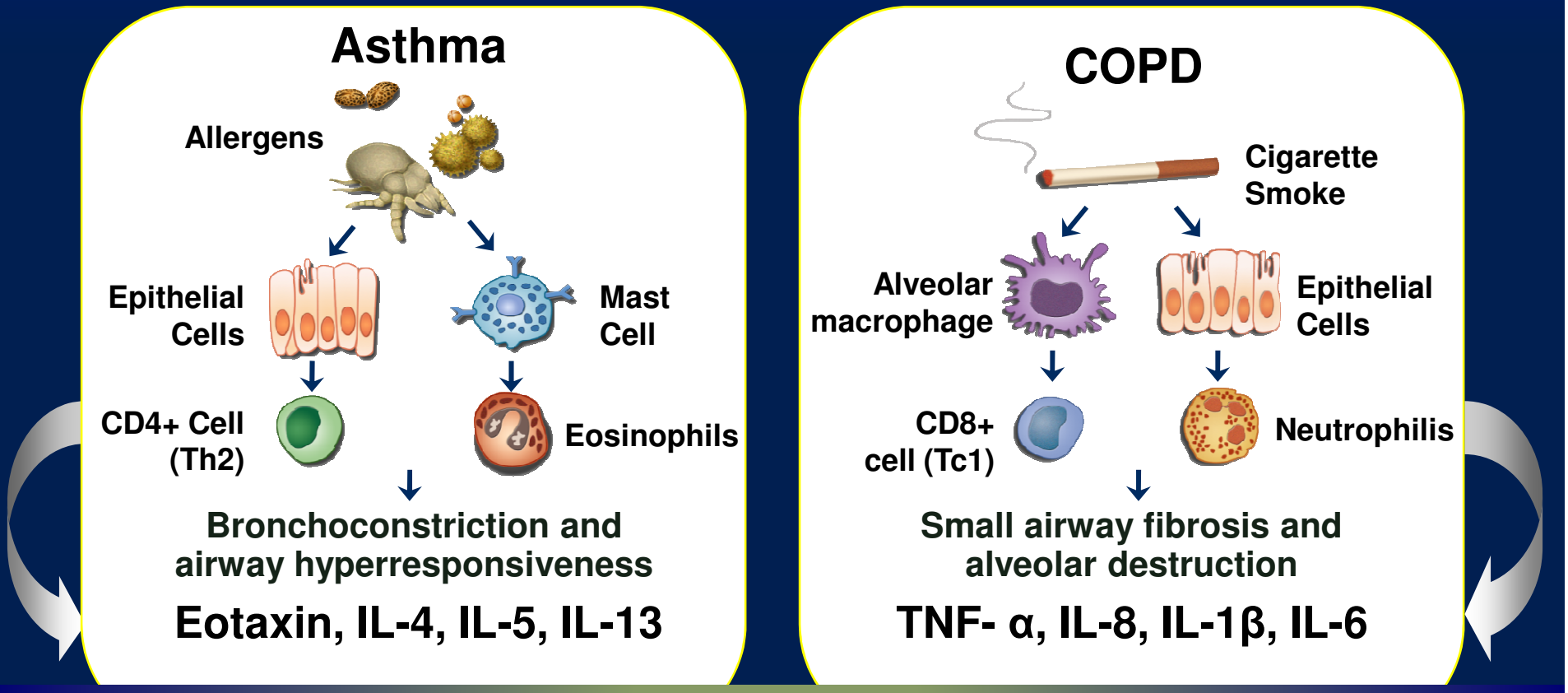
Inflammatory Cascade Differs Between Asthma and COPD

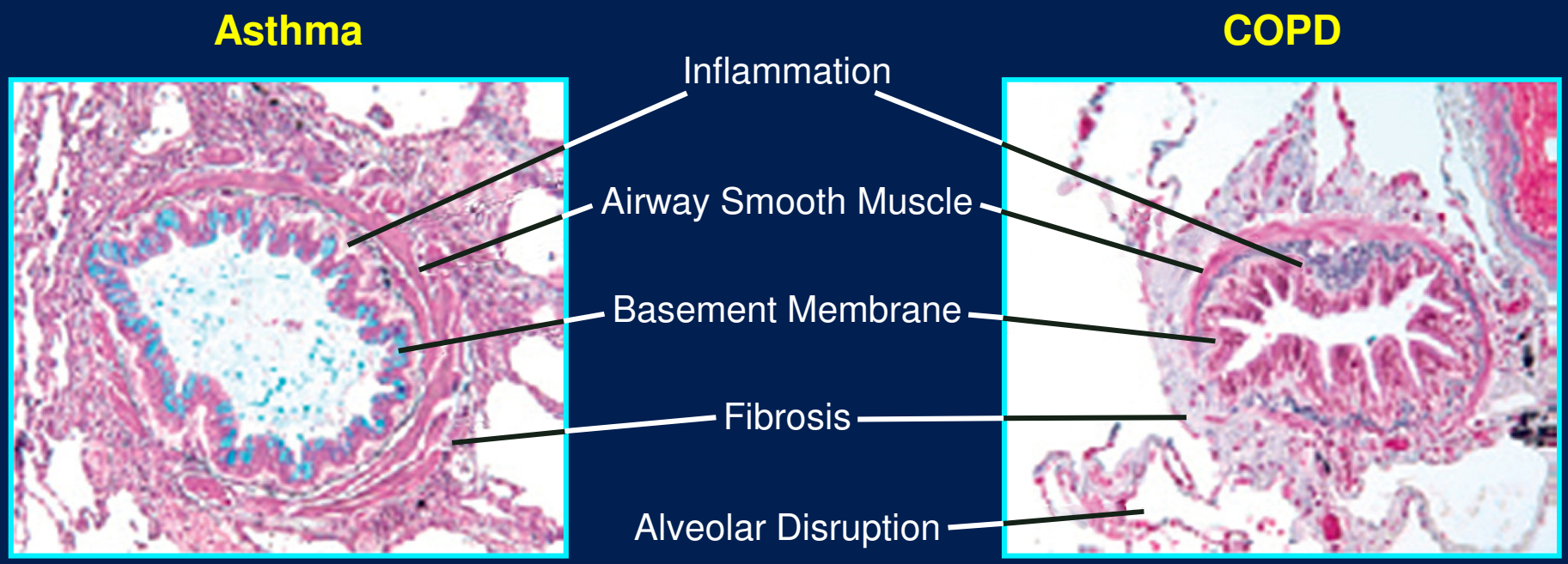


IL = interleukin; TNF = tumor necrosis factor.

Adapted from Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989. Accessed November 21, 2008.

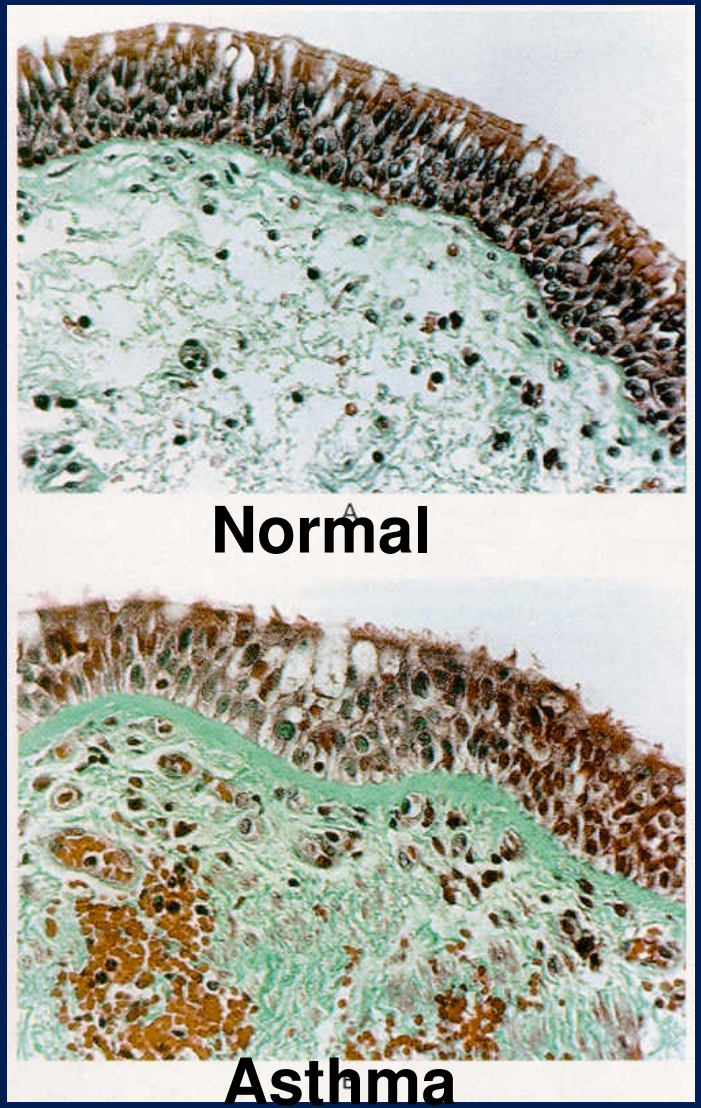
Pathophysiological Changes in Asthma and COPD

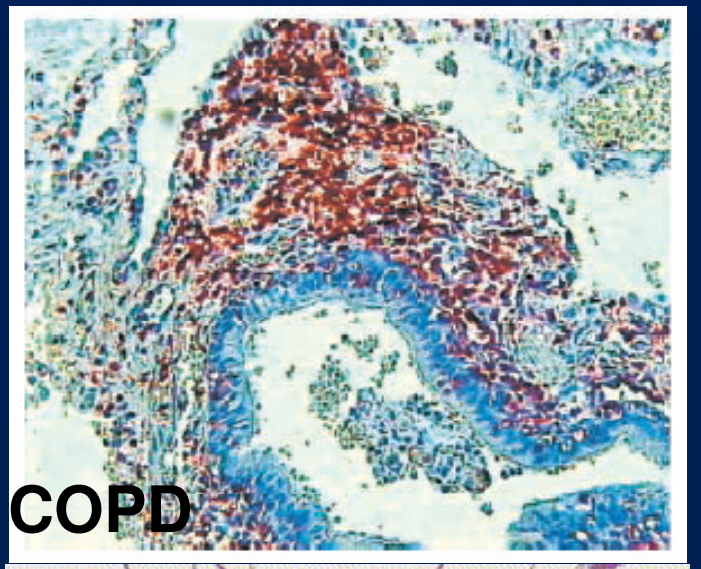
Contrasting Histopathology of Asthma and COPD

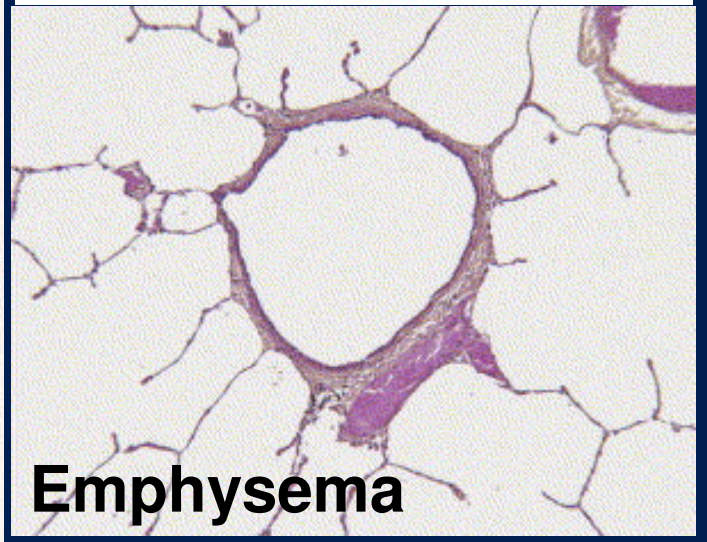


Adapted with permission from Barnes PJ. *Nature Rev Immunol.* 2008;8:183-192.

Structural Changes in Asthma and COPD







Inflammatory Phenotypes in Asthma vs. COPD

Asthma

- Eosinophils and mast cells
- Neutrophils (severe)
- CD 4+ T_H2 cells
- LTC4, D4, E4
- Cytokines
  - IL 4, IL 5, IL 13
  - RANTES, eotaxins, MCP-1

COPD

- Macrophages and neutrophils
- Eosinophils (exacerbations)
- CD 8+ T cells,
- LTB4, Interferon γ
- Cytokines
  - IL 8, IL-1
  - TNF-α

Fabbri, et al. Am J Respir Crit Care Med 2005; Vol 171: 686-698,

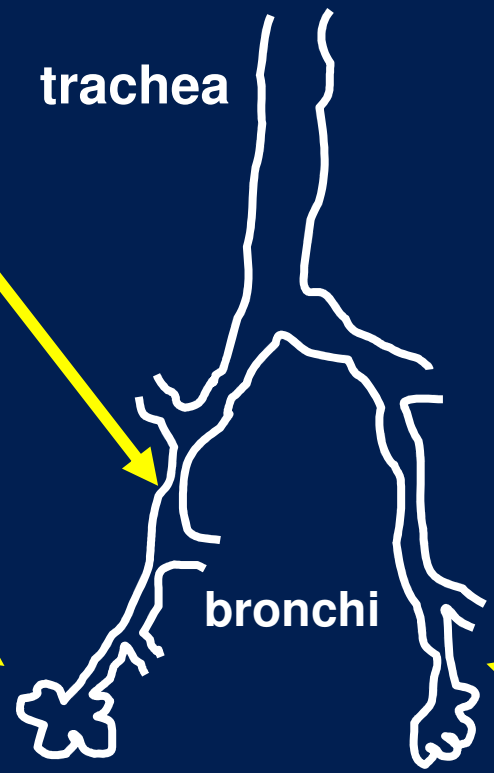
Sutherland. J Allergy Clin Immunol 2004; Vol 114 (4): 715-724

Mauad T, Dolhnikoff M. Curr Opin Pulm Med 2008; 14: 31 - 38

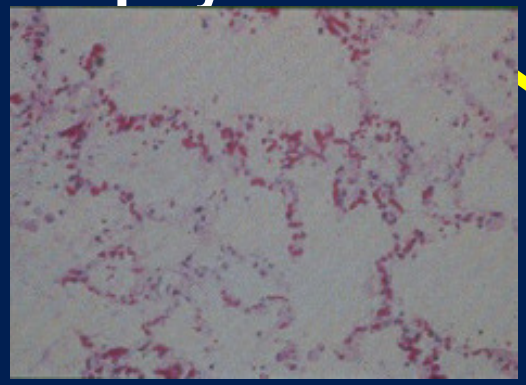
Site of Airway Obstruction in Asthma and COPD:

Asthma in Medium Sized Airways, COPD in the Small Airways

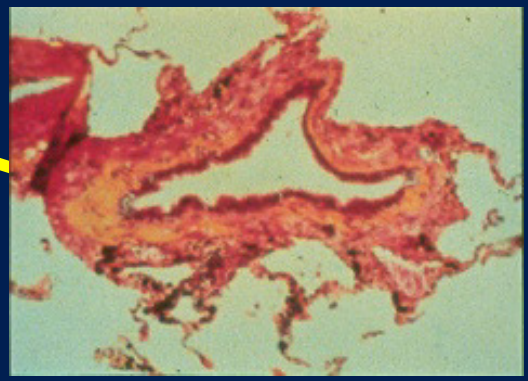
Asthma



Emphysema



Chronic Bronchitis



However,

- **Asthma is often progressive process with partially reversible component that can involve small peripheral airways**
- **CT scans demonstrating increased airway wall thickness like COPD**
  - Volume of lung in density range c/w emphysema: 5% in mild and 23% severe asthmatics

Sciurba FC Chest 2004:126:17S

Inflammation- Similarities

1. **Alveolar inflammation demonstrated in asthma ***
2. **Severe asthma- BAL with neutrophils ****
3. **COPD: tissues eosinophils during exacerbations**
   - Pts with eosinophils have better response to steroids ***

* Kraft M.Am J Respir Crit Care.Med 1996:154:1505

**Wenzel S Am J Respir Crit Care Med:1999:160:1001

***Chanez P Am J Respir Crit Care Med 1997:155:1529

Pathophysiology of Asthma

- **Inflammation in asthma is characterized by eosinophils, CD4+ T-lymphocytes, macrophages and mast cells**
- **Prominent pathological features of asthma include:**
  - airway hyperresponsiveness
  - episodic bronchospasm in the large airways
  - vasodilation and angiogenesis
- **Severe asthma can be classified into two subtypes: eosinophil (+) and eosinophil (-)**
- **Neutrophils are found in severe, corticosteroid-dependent asthma**

Pathophysiology of COPD

- **COPD is a disease characterized by inflammation in:**
  - airways
  - systemic circulation
- **COPD is a systemic disease that can cause weight loss and muscle weakness**
- **Prominent pathological features of COPD include:**
  - mucus hypersecretion
  - small airway fibrosis
  - alveolar destruction
  - extrapulmonary effects

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- **Pulmonary function and disease progression**
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Pulmonary Function

- **Classically**
  - Asthma reversible airway obstruction
  - COPD partially reversible

Boulet L Can Respir J 1998:5:270
Fabbri LM Am J Respir Crit Care Med 2003:167:418
Magnussen H. Clin Exp Allergy 1998 28:187

Spirometry Is Essential in Both Asthma and COPD

Asthma

- **Necessary to establish a diagnosis[1]**
- **Low FEV_1 is strongly predictive of risk for exacerbations[1,2]**
- **Important in assessing control[1]**

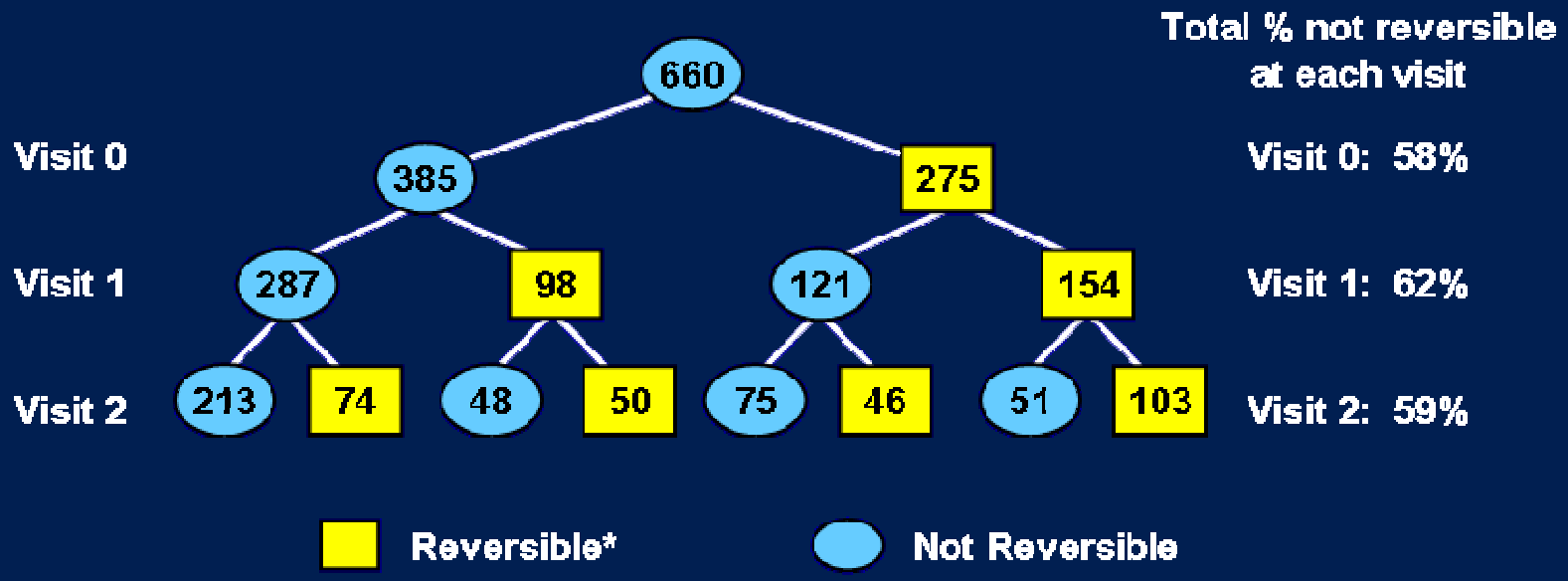
COPD

- **Essential for diagnosis[3]**
- **Used to determine severity, which is linked to**
  - Treatment decisions
  - Prognosis

1. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
2. Fuhlbrigge AL et al. *J Allergy Clin Immunol*. 2001;107:61-67.
3. Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989.

Acute Bronchodilator Response Does not Differentiate Between Asthma and COPD:

Changes in Responder Classification After Albuterol and Ipatroprium Bromide



Numbers in circles refer to the total classified as positive responders at that visit and those in squares are the nonresponders on the same occasion.

* Reversible defined as ≥ 12% and 200-mL increase in FEV_1 following 4 puffs (360 mcg) of albuterol.

Calverley et al. *Thorax*. 2003;58:659-664.

Physiologic Differences Between Asthma and COPD

	Asthma	COPD
Elastic recoil	Normal	Decreased
Diffusion capacity (DL_{CO})	Normal or Increased	Decreased
Lung volume	Normal	Hyperinflation
Bronchodilator response	Flow-dominant	Volume-dominant

Sciurba FC. *Chest*. 2004;126:117S-124S.

Lung Volumes

- **Nonreversible COPD pts 83% had improvement in lung volumes**
  - Those with most severe disease > improvement
- **Asthma study 15% reversibility in lung volumes not FEV-1**

O'Donnel C Eur Respir J 2001:18:914

Smith HR Chest 1992:101:1577

Pulmonary Function

- **Comparing spirometry, lung volumes & DLCO in COPD vs incompletely reversible asthma (nonsmokers)**
  - DLCO best discriminator
    - COPD - 58-67% predicted
    - Asthma- 85-99% predicted
    - However, for individuals DLCO 80% predicted 77% sensitive and 71% specific in discriminating asthma from COPD

Boulet L Can Respir J 1998:5:270
Fabbri LM Am J Respir Crit Care Med 2003:167:418
Magnussen H. Clin Exp Allergy 1998 28:187

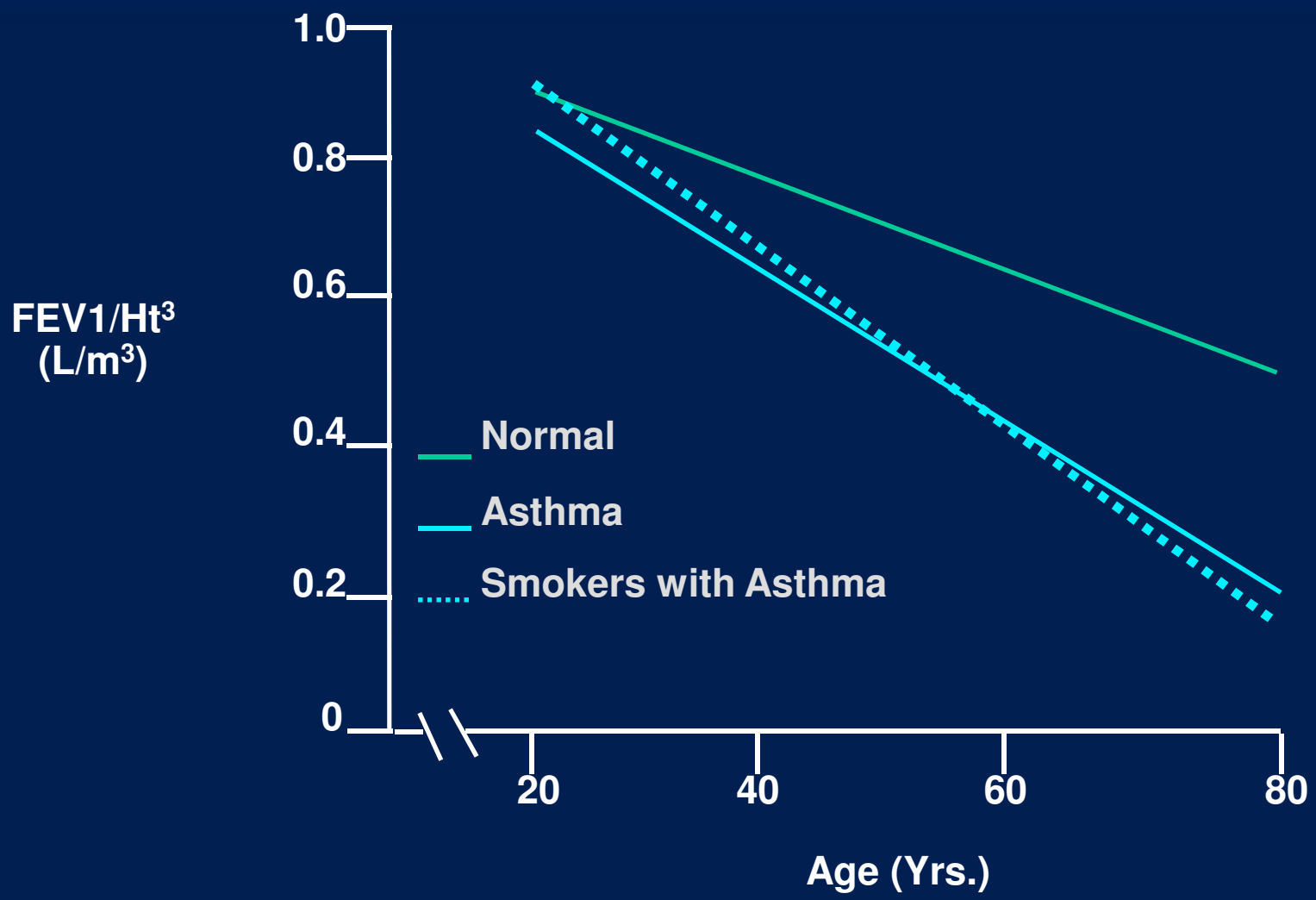
Airway Hyperresponsiveness

- **Positive Methacholine occurs in nearly all asthmatics, < 5% normals**
- **63% of men and 87% of women with COPD show AHR with < 25 mg/ml of metacholine**
  - Lower PFT'S associated with >AHR, decline in lung function and mortality
  - Smoking cessation has positive effect on AHR and improves FEV1 greater in those with AHR

Tashkin D An J Crit Care Med 1996:153:1802

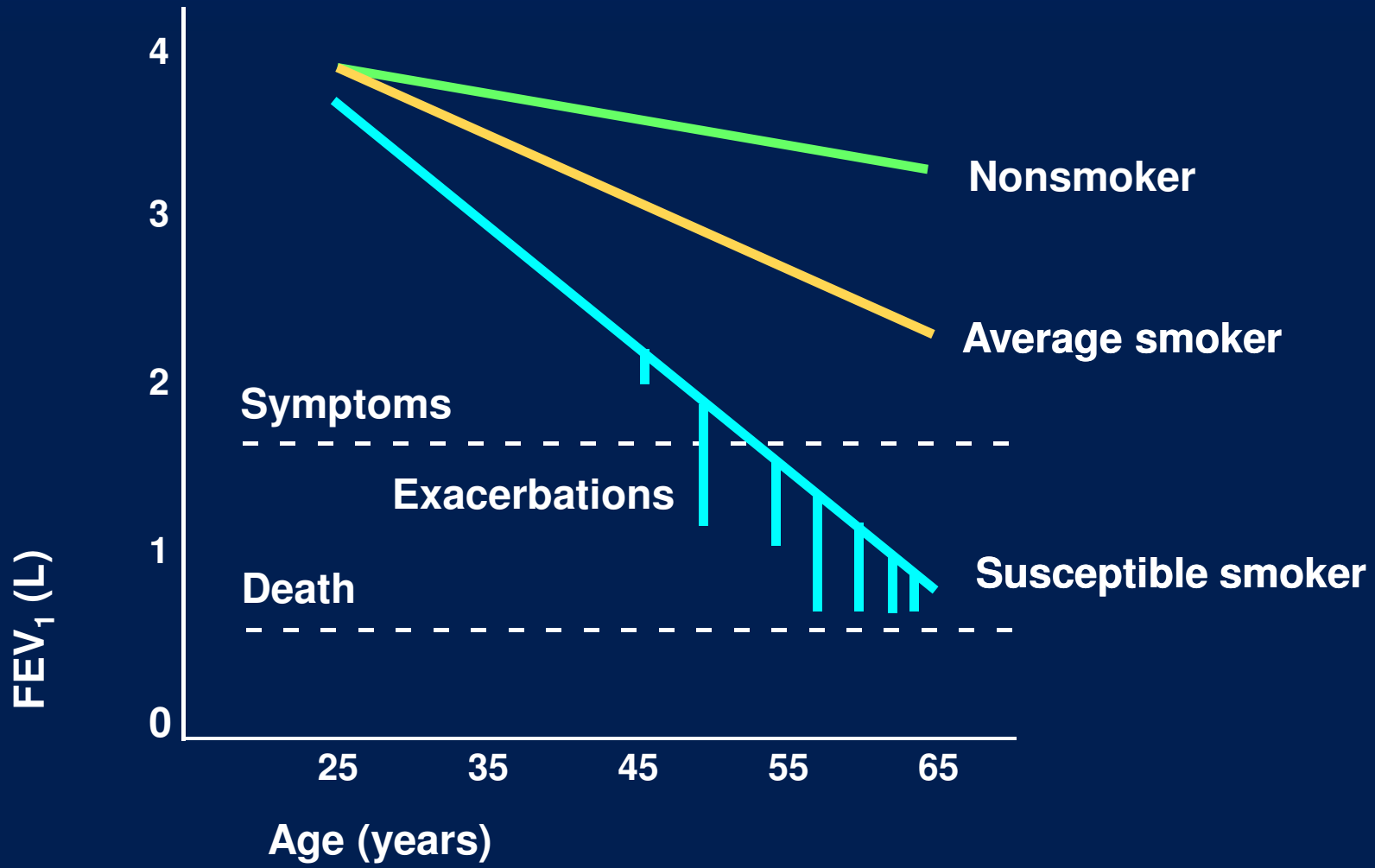
Wise RA et al. Chest 2003; 12: 4:449- 458

Natural History of Asthma



Peat JK. Eur J Respir Dis. 1987

Natural History of COPD



Mannino DM. *Chest.* 2002;121:121S-126S.

Fletcher and Peto, 1977

Physiologic Differences

Asthma

- Normal DLCO
- Normal lung volume
- Normal elastic recoil
- Flow dominant BD response

COPD

- Abnormal DLCO
- Hyperinflation
- Decreased elastic recoil
- Volume dominant BD response

Sciurba FC, CHEST 2004;117S-124S

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The Clinical Spectrum of Asthma and COPD

- **Asthma**: Symptoms caused by variable airflow obstruction that may be progressive
- **COPD**: Symptoms caused by chronic (progressive) airflow obstruction with superimposed exacerbations

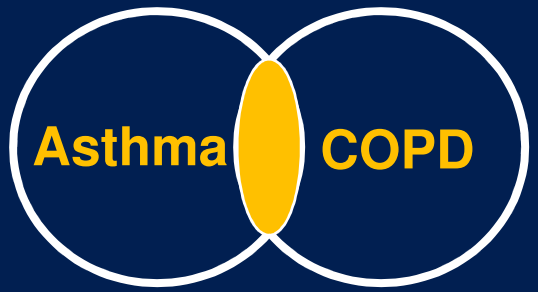
GOLD Guidelines 2003. Available at: www.goldcopd.com/revised.pdf.

Key Differences in Clinical Presentation Between Asthma and COPD

-

COPD

- Onset in mid-life.
- Symptoms slowly progressive.
- Long smoking history.
- Dyspnea during exercise.



Asthma

- Onset early in life (often childhood).
- .Symptoms vary from day to day.
- .Symptoms at night/early morning.
- .Allergy, rhinitis, and/or eczema also present.
- .Family history of asthma.

Asthma Imitates Mild/Moderate COPD With Increasing Age

Asthma in young age

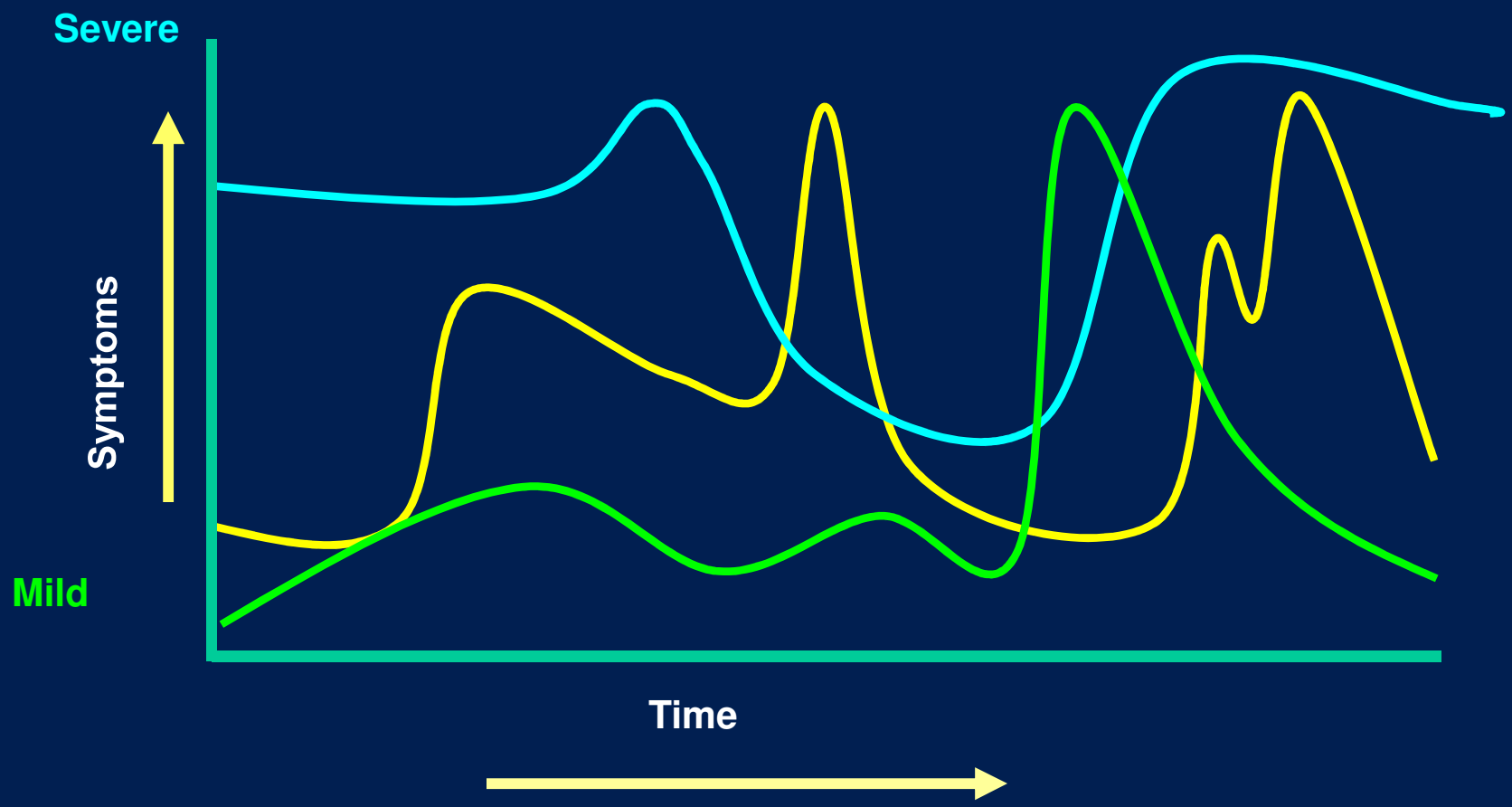
- ±80% extrinsic
- Often normal FEV_1
- Often reversible obstruction
- Remission likely (60%–70% patients)

Asthma in old age

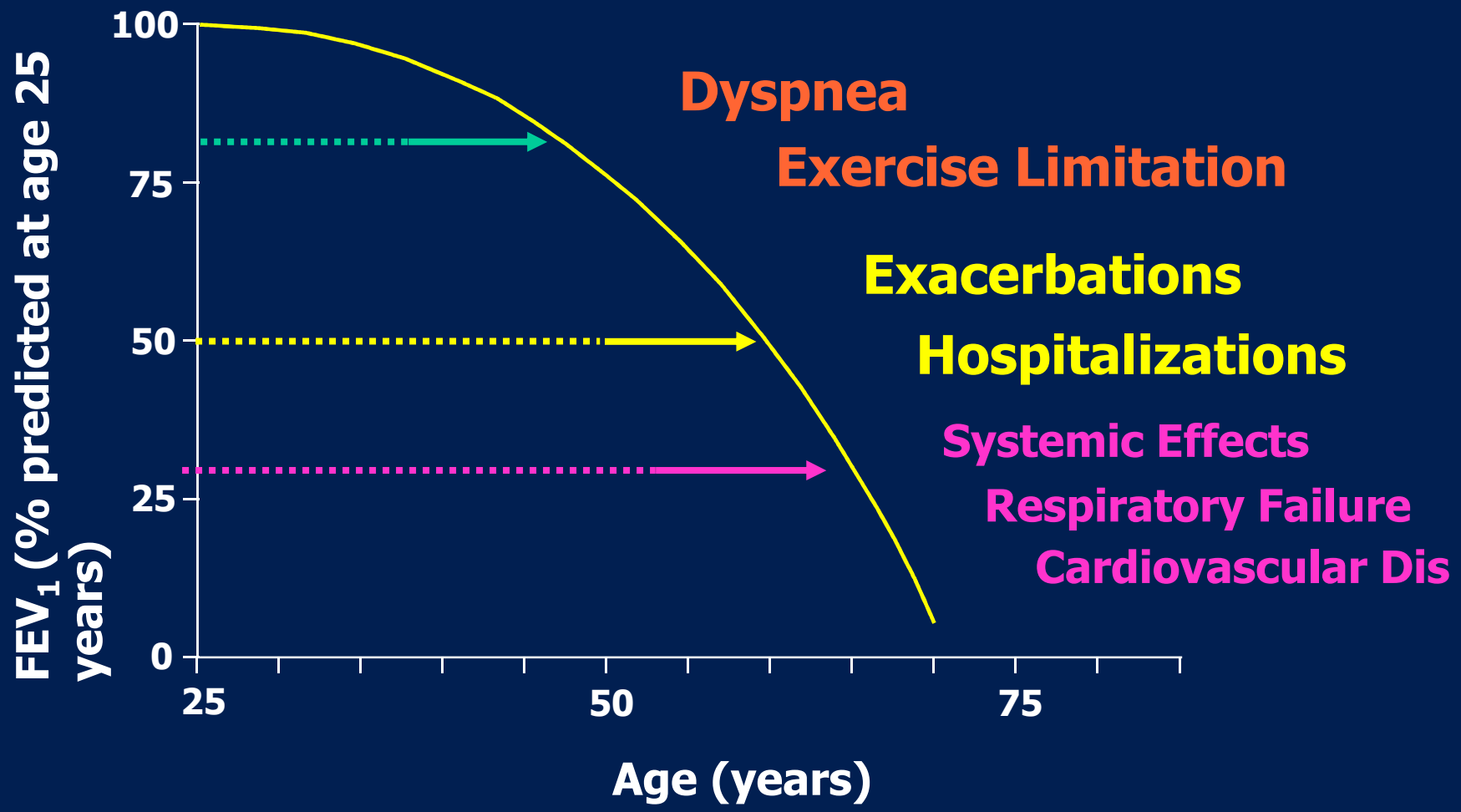
- Mainly intrinsic
- Often reduced FEV_1 (60% of patients)
- Often less reversible obstruction
- Remission unlikely (20% patients)

Braman SS. *Clin Geriatr Med.* 2003;19:57-75.

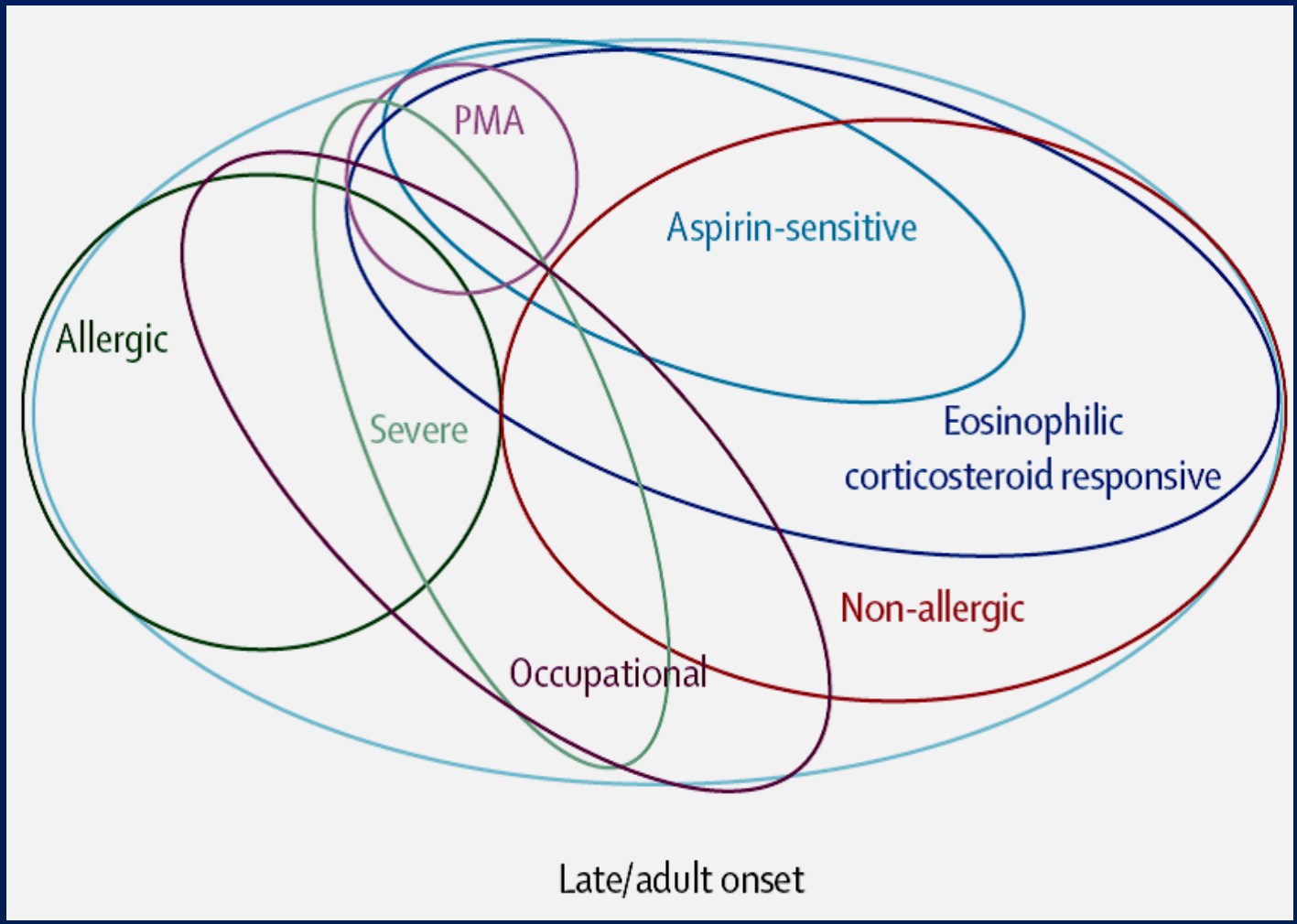
Asthma Clinical Course



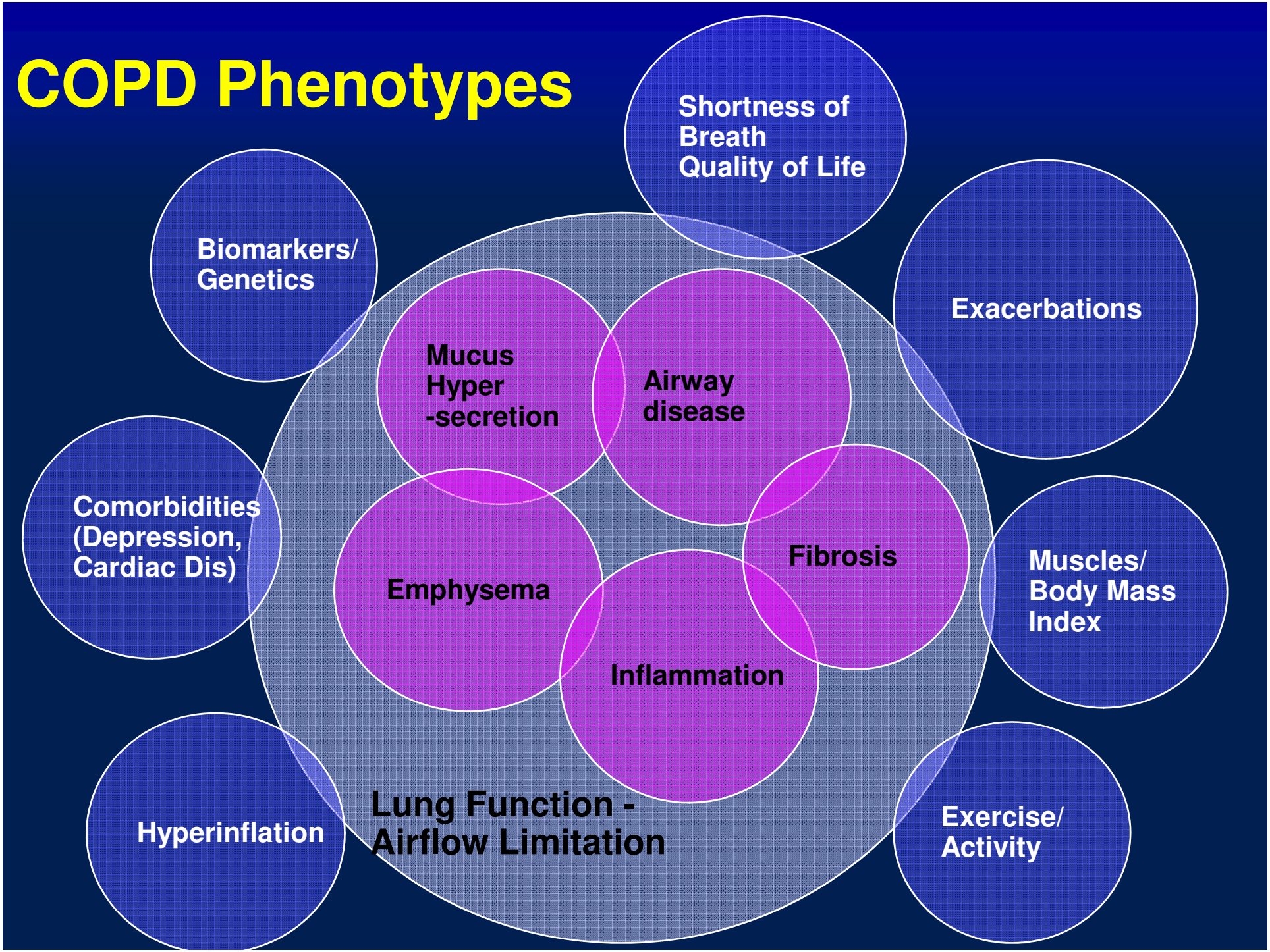
COPD: Clinical Course



Asthma: Definition of Adult Phenotypes

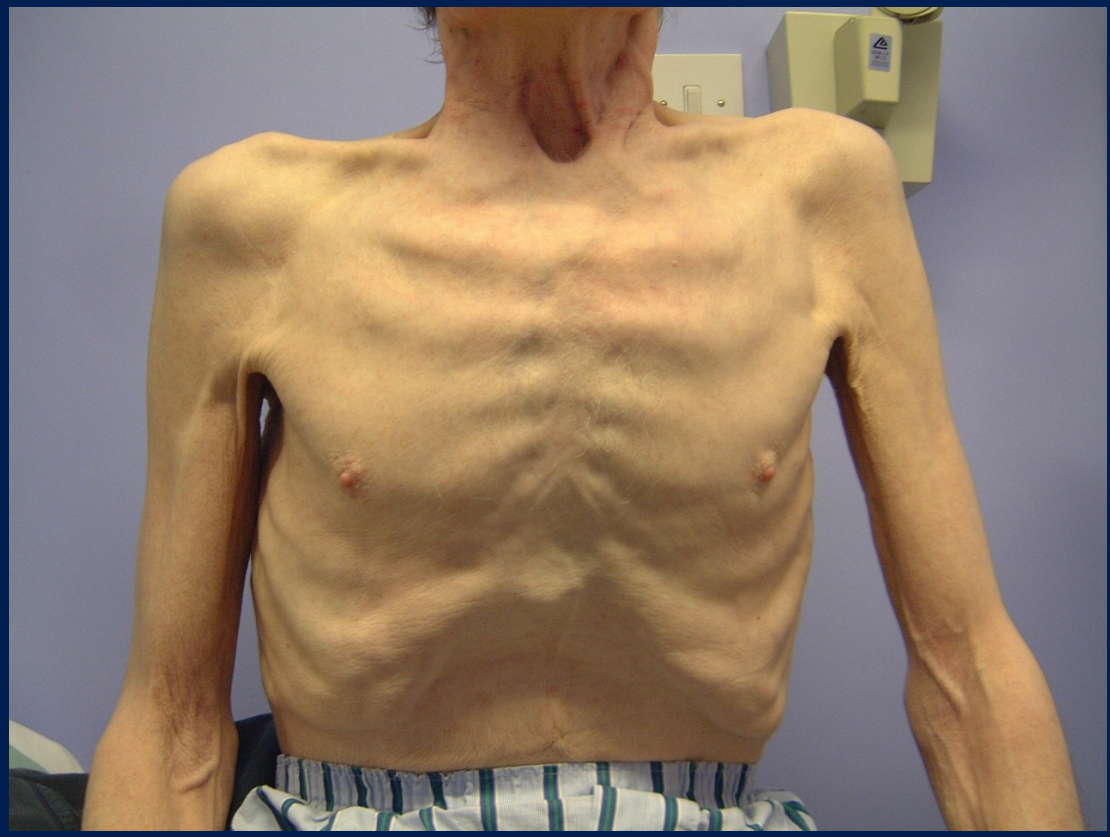


Wenzel SE. Lancet 2006;368:804-813


COPD Phenotypes
Shortness of Breath Quality of Life
Biomarkers/ Genetics
Exacerbations
Mucus Hyper -secretion
Airway disease
Comorbidities (Depression, Cardiac Dis)
Fibrosis
Muscles/ Body Mass Index
Emphysema
Inflammation
Hyperinflation
Lung Function - Airflow Limitation
Exercise/ Activity

Systemic Consequences of COPD

- Weight loss with decreased fat-free mass
- Muscle wasting and weakness
- Cardiac co-morbidity
- Other systemic effects:
  - osteoporosis
  - anemia
  - depression



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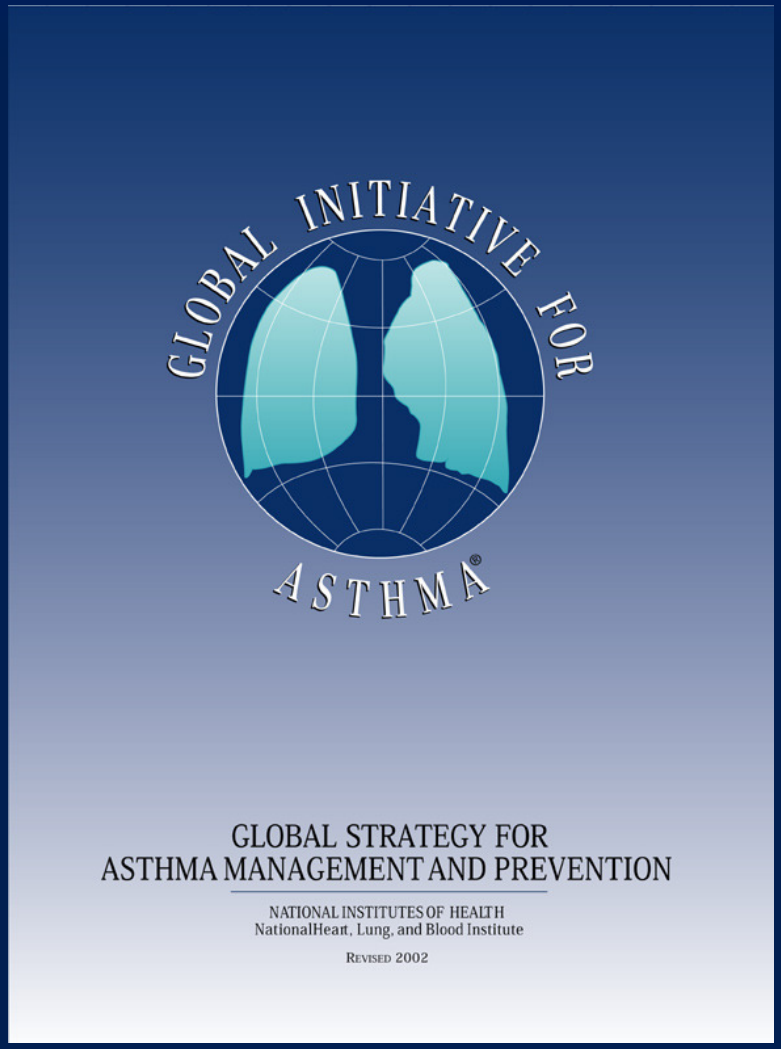
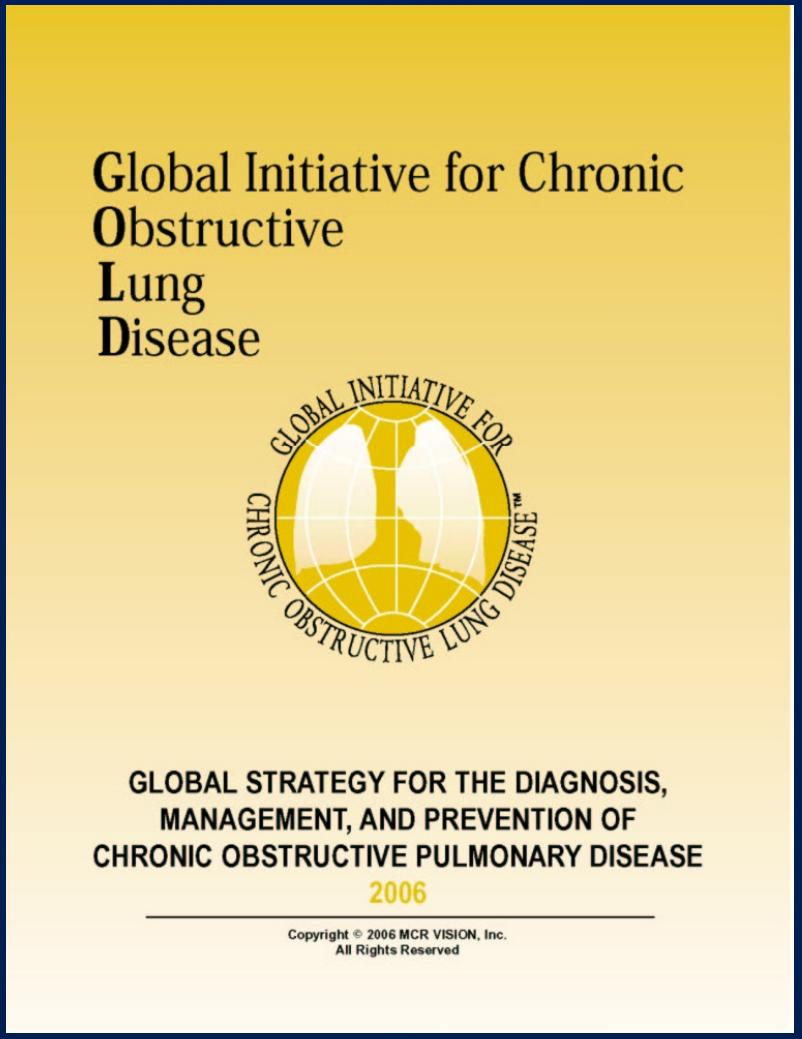
GINA


GLOBAL INITIATIVE FOR ASTHMA®
GLOBAL STRATEGY FOR
ASTHMA MANAGEMENT AND PREVENTION
NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute
REVISED 2002

GOLD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GINA: Levels of Asthma Control

Characteristic	Controlled (All of the following)	Partly controlled (Any present in any week)	Uncontrolled
Daytime symptoms	None (2 or less / week)	More than twice / 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	None (2 or less / week)	More than twice / week	
Lung function (PEF or FEV_1)	Normal	< 80% predicted or personal best (if known) on any day	
Exacerbation	None	One or more / year	1 in any week

COPD Staging: GOLD Guidelines

GOLD Stage	Symptoms	FEV_1/FVC*	FEV_1 (Predicted)*
I: Mild	**+/–**	**<70%**	**≥80%**
II: Moderate	**+/–**	**<70%**	**≥50%, <80%**
III: Severe	**+/–**	**<70%**	**≥30%, <50%**
IV: Very severe†		**<70%**	**<30%**

***Postbronchodilator values.**
†Or FEV_1 <50% plus chronic respiratory failure.

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
Pauwels R, et al. Available at: http://www.goldcopd.com.

GOALS OF THERAPY

COPD

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

Asthma

- Achieve normal lung function
- No symptoms
- Maintain normal quality of life
- Prevent and treat exacerbations
- Prevent mortality

Nonpharmacologic Approaches

ASTHMA

- Identifying and avoiding triggers
  - Allergens, irritants (smoke)
- Vaccination
- Treat underlying conditions that may result in asthma control
  - Allergic rhinitis, sinusitis, gastroesophageal reflux (GERD)
- Asthma education

COPD

- All stages of disease
  - Smoking cessation
  - Avoidance of indoor and outdoor occupational exposures
- Vaccinations
- Optimizing nutrition
- Oxygen
- Pulmonary rehabilitation
- Surgical interventions (LVRS, transplantation)

Pharmacologic Therapy

- Two different sets of guidelines
- Two different treatment paradigms
- Similar pharmacologic agents

Medications for Asthma and COPD

Asthma

Anti-inflammatory drugs

- Corticosteroids
- Antileukotrienes
- Cromones
- Theophylline (?)

Bronchodilators

- Short and Long-acting ß-agonists
- Short-acting Anticholinergic

ICS/LABA combination

Anti IgE

COPD

Bronchodilators

- Short and Long-acting ß-agonists
- Short and Long-acting Anticholinergics
- Theophylline

Anti-inflammatory drugs

- Corticosteroids

ICS/LABA Combination

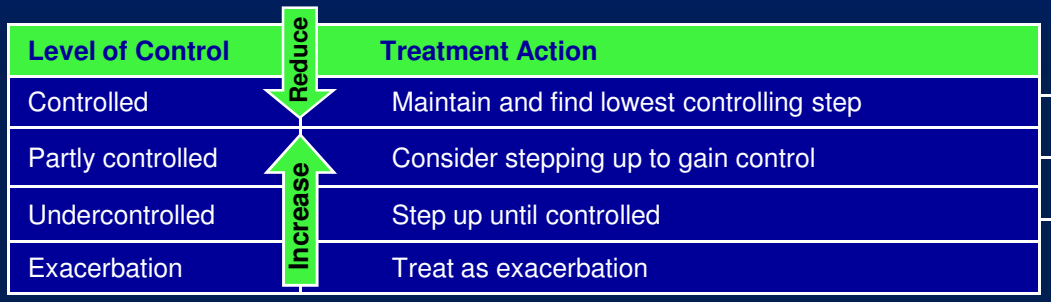
Mucoactive drugs

Antibiotics

Vaccination

GINA Management Approach Based on Control

Children Aged >5 Years, Adolescents, and Adults



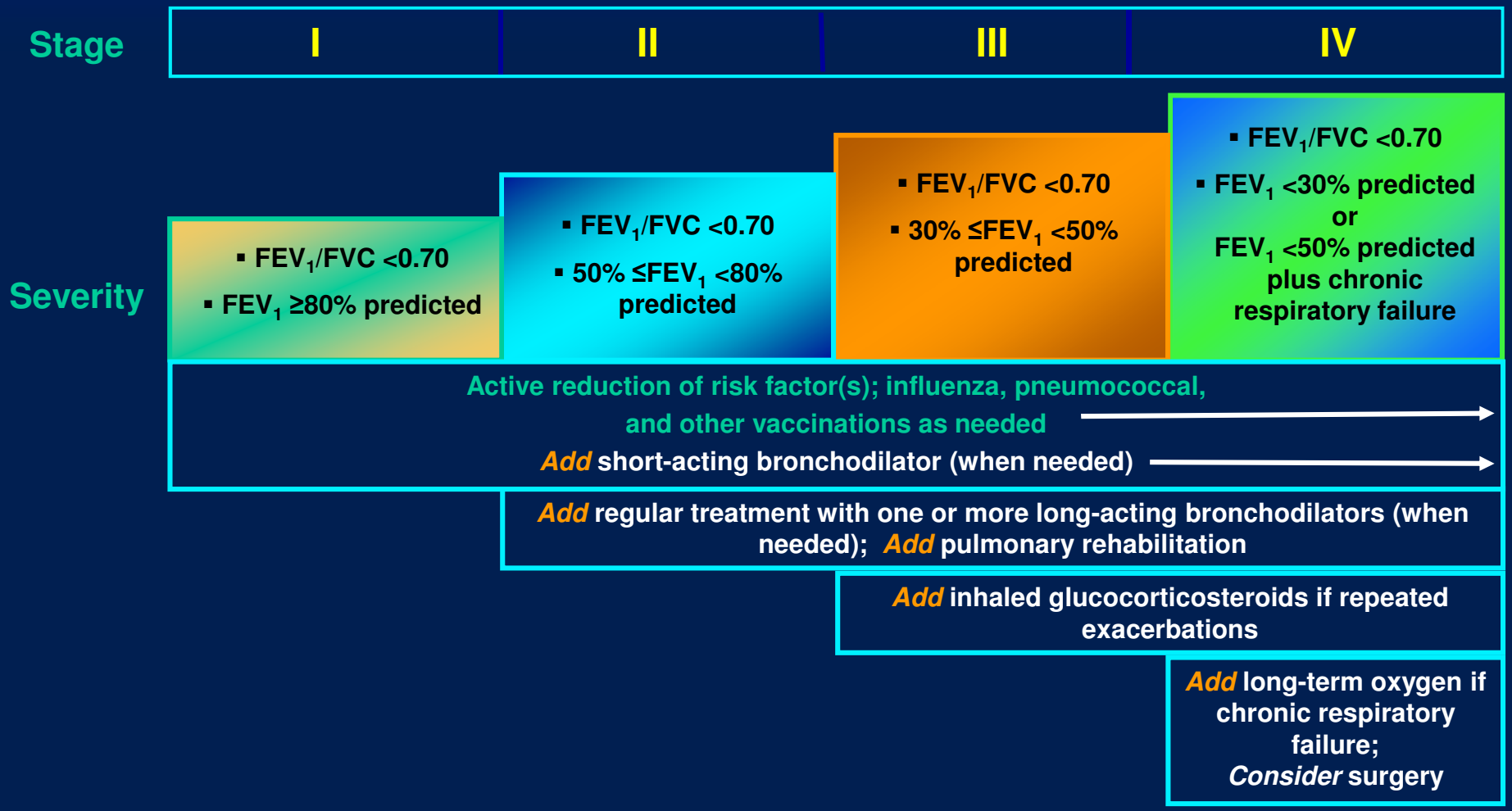
Reduce ← **Treatment Steps** → **Increase**

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma Education Environmental Control				
As-needed rapid-acting β_2-agonist	As-needed rapid-acting β_2-agonist			
Controller options	**Select one**	**Select one**	**Add one or more**	**Add one or both**
	Low-dose inhaled ICS	Low-dose ICS plus LABA	Medium- or high-dose ICS plus LABA	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier	Medium- or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus leukotriene modifier	Sustained-release theophylline	
		Low-dose ICS plus sustained-release theophylline		

Alternative reliever treatments include inhaled anticholinergics, short-acting oral ß$_2$-agonists, some long-acting ß$_2$-agonists, and short-acting theophylline. Regular dosing with short- and long-acting ß$_2$-agonists is not advised unless accompanied by regular use of an inhaled glucocorticosteroid.

Global Initiative for Asthma. ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=60.

Gold Guidelines
Stepwise Approach for Managing COPD



Adapted from Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003.

Response to Bronchodilators

- **ASTHMA**
  - SABA
    - Tolerance
    - Dosed PRN
  - LABA
    - Monotherapy assoc. with increased frequency of exacerbations
    - Little tolerance
  - Anticholinergic
    - Efficacious in acute attack
- **COPD**
  - SABA
    - No tolerance
    - Regularly dosed
  - LABA
    - Monotherapy assoc. with decreased frequency of exacerbations
    - Little tolerance
  - Anticholinergic
    - Efficacious in acute and stable disease

Donohue JF, CHEST 2004;125S-137S

Response to Inhaled corticosteroids

- **ASTHMA**
  - First line therapy even in mild persistent disease
  - Improve lung function and symptoms and health status, decrease exacerbations,
  - Decrease mortality
  - Significant anti-Inflammatory effects
  - Decreased response in smokers
- **COPD**
  - Modest effect on long-term deterioration in lung function
  - Significant decrease in exacerbations (30%)
  - Significant improvement in health status
  - No effect on mortality
  - Recommended by guidelines for severe disease and in patients with recurrent exacerbations
  - ? Increase risk of pneumonia

Acute Exacerbations of Asthma & COPD

Differences in Management of Acute Asthma and COPD

- Acute Asthma
  - Mostly treated in ED or outpatient
  - Short-acting bronchodilators
  - Systemic corticosteroids
  - Oxygen therapy
  - No need for antibiotics
  - Non-invasive ventilation usually not effective
- Acute COPD
  - Low threshold for admission
  - Short-acting bronchodilators
  - Systemic corticosteroids
  - Controlled oxygen therapy
  - Antibiotics
  - Non-invasive ventilation
    - Level A indication

Novel Therapeutic Targets: Asthma

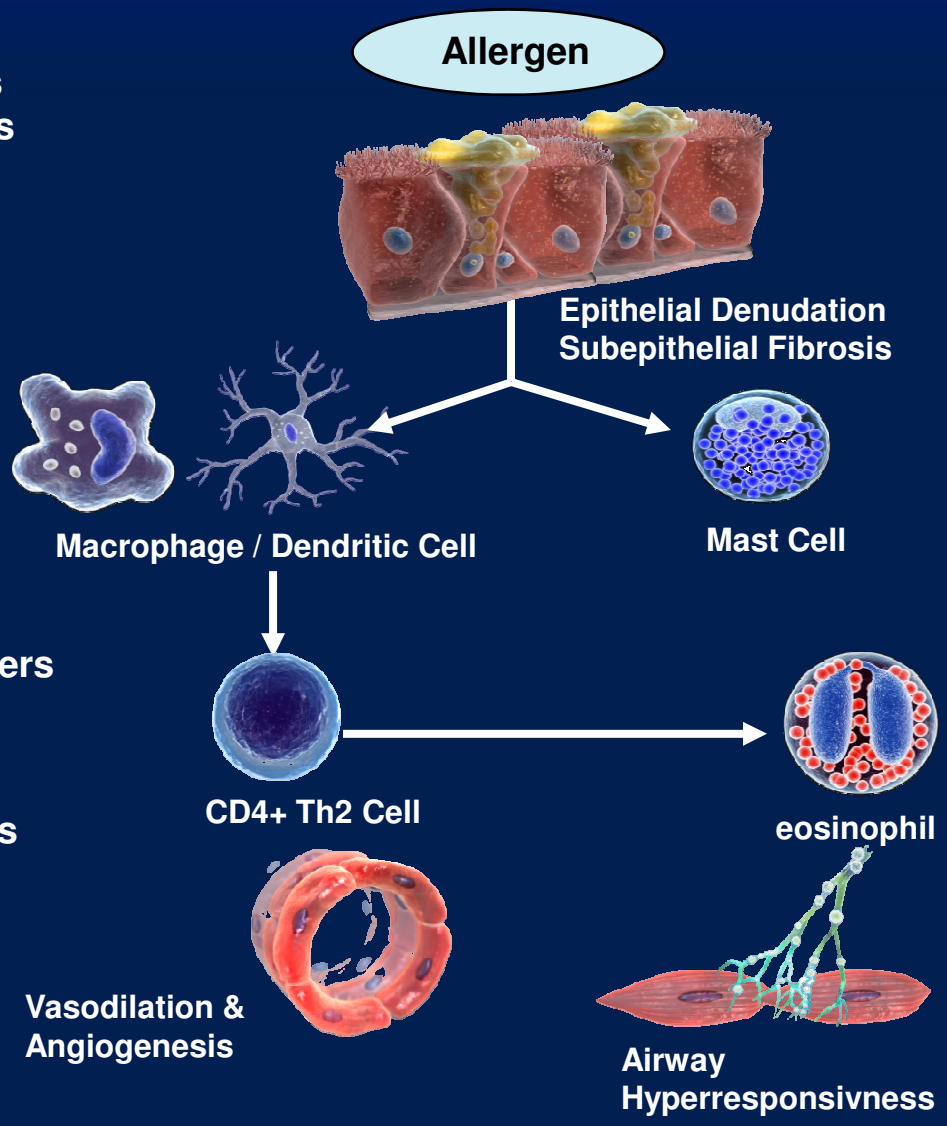
New Corticosteroids
New Bronchodilators

PDE4 Inhibitors

Transcription Factor & Kinase Inhibitors
- NF-κB
- NF-AT
- GATA3
- P38 MAP kinase
- JNK
- Syk

Cell Adhesion Blockers
- ICAM1
- VLA4

Mediator Antagonists
- antihistamines
- leukotriene
- prostaglandins
- endothelin
- adenosine
- tryptase
- NO



Immunotherapy
- Specific AG
- T-cell peptides
- BCG, CpG

Anti-Allergy Drugs
- anti-IgE
- anti-CD23

Interleukin Inhibitors
- IL-5, 4, 13
- IL-9
- IL-1

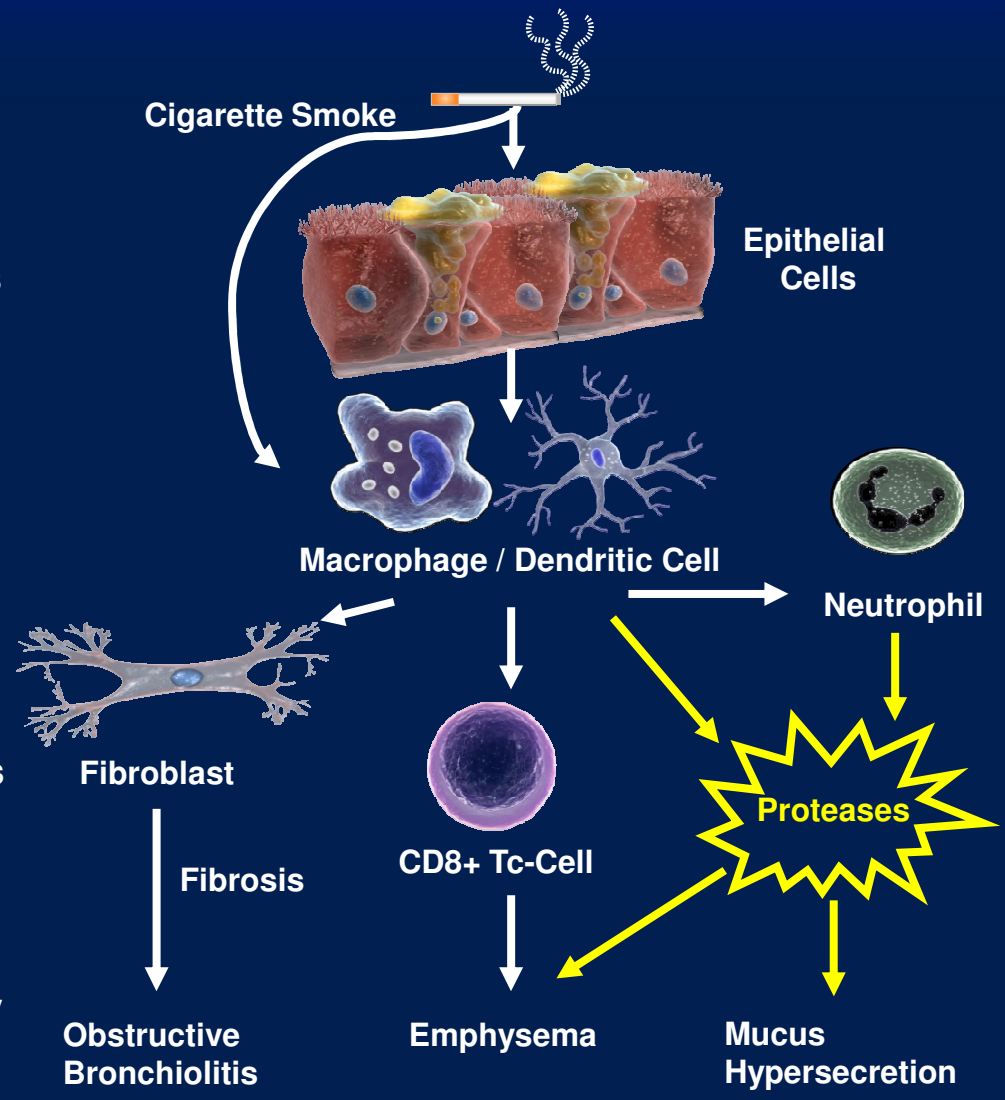
TNF-α Inhibitors

Cytokines
- IL-10
- IFN-γ
- IL-12/18

Chemokine Receptor Inhibitors
- CCR2, 3, 4 & 8

Barnes PJ. *Nature Reviews* 2004; 3: 831–44.

Novel Therapeutic Targets: COPD



Smoking Cessation

New Bronchodilators

PDE4 Inhibitors

Transcription Factor & Kinase Inhibitors
- NFKB
- P38 MAPK
- PI3Kγ

Mediator Antagonists
- CXCR2
- CCR2
- TNF-α

Anti-Fibrotic Therapy
- TGF-β1

Anti-Oxidants
iNOS Inhibitors

Protease Inhibitors
- NE
- MMP
- SLPI
- α_1-AT

Muco-Regulators
- EGF rec kinase

Alveolar Repair
- retinoids

Barnes PJ & Hansel TT. *Lancet* 2004; 364: 985–996.

Similarities Between Asthma and COPD

Differences Between Asthma and COPD

Asthma

- Usually intermittent airflow obstruction but sometimes has a less reversible obstruction
- High levels of bronchial responsiveness
- Cellular inflammation with eosinophils, mast cells, T lymphocytes, in severe disease neutrophils
- Broad inflammatory mediator responses
- Airway remodeling (epithelial injury and fibrosis)
- Significant response to corticosteroids
- Improvement in airway obstruction with bronchodilators and corticosteroids

COPD

- Progressive airflow obstruction
- Most patients have increased bronchial responsiveness
- Cellular inflammation including neutrophils, macrophages, eosinophils and mast cells may occur in exacerbations
- Cytokine, chemokine, protease responses
- Emphysema (lung destruction) frequent
- Poor response to ICS
- Smaller bronchodilator and corticosteroid response
- Systemic consequences

DISTINCT AND SEPARATE DISEASES

Bleecker ER. *Chest.* 2004;126(suppl 2):93S-95S.