Moving from the Oslerian Paradigm to Post-genomic Era: Are Asthma and COPD Outdated Terms?

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THE LIFE SPECTRUM OF ASTHMA

JULY 29-31 CHICAGO, IL 2016

AMERICAN LUNG ASSOCIATION. ACRC NETWORK Airways Clinical Research Centers

Disclosure Information

- Advisor/Consultant:
  - Roche (Genentech), AstraZeneca, Boehringer Ingelheim, Sunovion, Novartis, Mylan
- Research grant support (to institution):
  - National Heart, Lung, and Blood Institute, American Lung Association
  - GSK, Boehringer Ingelheim, Genentech, Sunovion, Mylan, Pearl Therapeutics, Chiesi

Outline

- ✓Revisiting the Dutch Hypothesis: Do Asthma and COPD Represent a Continuum of One Disease?
- ✓Similarities and Differences Between Asthma and COPD: Problems with the Traditional Approach
  - ✓Risk factors/ Clinical Presentation and Course
  - ✓Pathologic Mechanisms
  - ✓Physiology
  - ✓Management
- ✓Is Asthma COPD Overlap Syndrome (ACOS) the Solution?

The "Dutch" Hypothesis

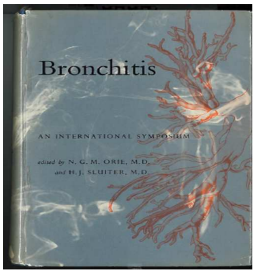
The "Dutch" Hypothesis

Common Disease?

Professor Dick Orie
Groningen, NL

Common Mechanisms

Asthma ……CNSLD……..COPD



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

The "Dutch"Hypothesis

Host (Genetic) factors

(Atopy, AHR)

Endogenous factors

(Sex, age)

Environmental factors

(Allergens, infection, smoking, air pollution)

Bronchial Inflammation

Asthma

CNSLD

COPD

Orie et al. Bronchitis II Second International Symposium. Assen, Netherlands: Royal Van Gorcum; 1964:398-99
Postma DS, Boezen HM. Chest 2004; 126: 96-104S
Postma DS et al. J Allergy Clin Immunol 2015; 136:521 -9

The "Dutch" Hypothesis

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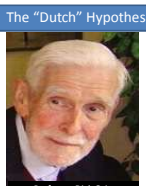

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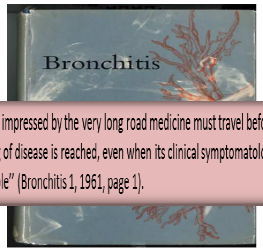
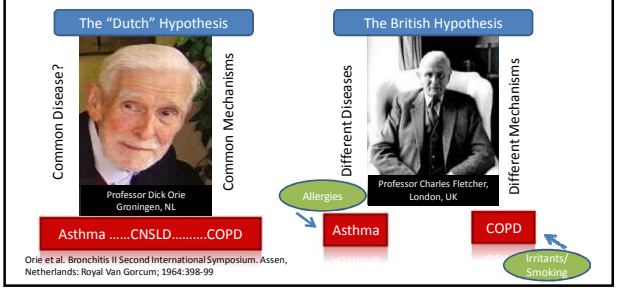


"one must be impressed by the very long road medicine must travel before an understanding of disease is reached, even when its clinical symptomatology is relatively simple" (Bronchitis 1, 1961, page 1).

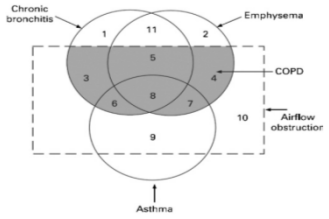
Orie et al. Bronchitis II Second International Symposium. Assen, Netherlands: Royal Van Gorcum; 1964:398-99

The Debate Continues…



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

The Overlap Between Asthma and COPD Traditional View



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.

What Is Asthma?

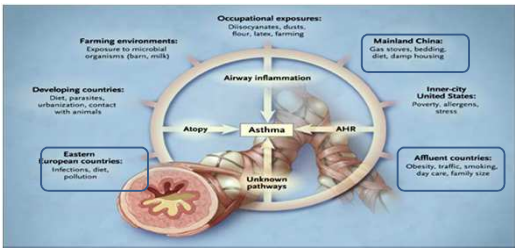
- A chronic inflammatory disorder of the airways in which many cells and factors play a role
- Inflammation results in
  - Recurrent symptoms
  - Variable airflow obstruction that is mostly reversible
  - Increase in existing bronchial hyperresponsiveness

What Is COPD?

- 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.
2. Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org

Asthma and COPD Share Some Common Environmental Risk Factors



Eder W et al., NEJM 2006;355:2226-2235

Risk / Precipitating Factors

Asthma

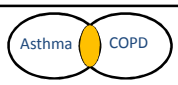
- Genetic susceptibility
- Airway hyperresponsiveness
- Obesity
- Environmental
  - Allergen exposures
  - Viral respiratory infections
  - Tobacco smoke and air pollution
- Disease triggers
  - Exercise
  - Changes in weather
  - Exposure to cold air
  - Emotional factors
  - Endocrine factors

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

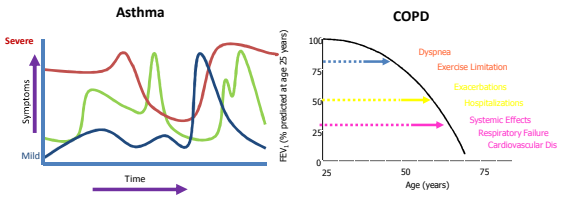
Clinical Presentation Between Asthma and COPD – Traditional View

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

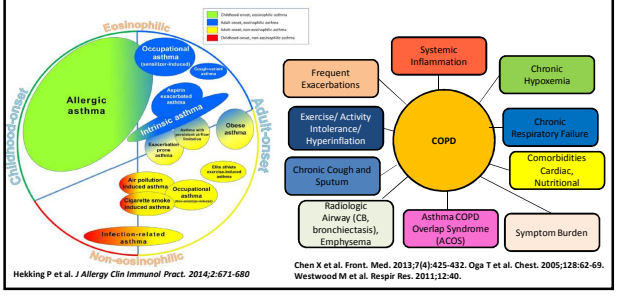


Asthma →
- Onset early in life (often childhood).
- Symptoms vary from day to day.
- Symptoms at night/early morning.
- Allergy, rhinitis, and/or eczema also present.
- Family history of asthma.

Clinical Course: Asthma vs. COPD



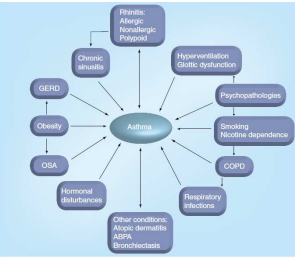
Phenotypes: Asthma vs. COPD



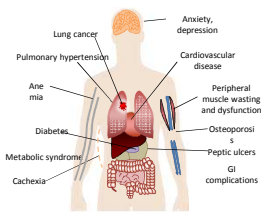
Hekking P et al. *J Allergy Clin Immunol Pract. 2014;2:671-680*

Chen X et al. Front. Med. 2013;7(4):425-432. Oga T et al. Chest. 2005;128:62-69. Westwood M et al. Respir Res. 2011;12:40.

Co-morbidities: Asthma vs. COPD



Boulet LP et al. Expert Rev. Respir. Med. 5(3), (2011)



Kao C, Hanania, NA. *Atlas of COPD*, 2008

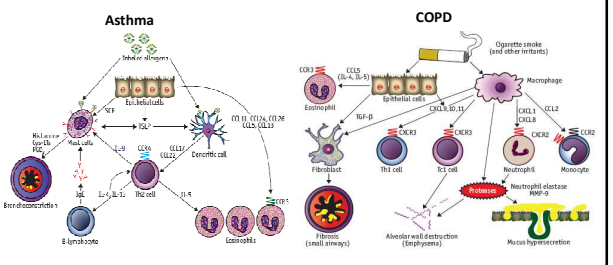
Traditional Approach in Differentiating Asthma and COPD – Clinical Presentation

Asthma	COPD
Onset early in life	Onset after age 40
Often atopic	Usually not atopic
Night and early morning symptoms Variable symptoms	Dyspnea with activity Progressive symptoms
Usually non-smokers	Smoker >10 pack.year
One phenotype	Blue bloater and pink puffer

Traditional Approach in Differentiating Asthma and COPD – Clinical Presentation

Asthma	COPD	Problem with the approach
Onset early in life	Onset after age 40	Asthma is frequently diagnosed in adults and older people (late onset)
Often atopic	Usually not atopic	Atopy also occurs in COPD and not in all people with asthma (30% are not)
Night and early morning symptoms Variable symptoms	Dyspnea with activity Progressive symptoms	Symptoms specific to the pathophysiological component of the disease rather than specific diagnosis
Usually non-smokers	Smoker >10 pack.year	25% of asthma patients smoke, high proportion of COPD patients are never smokers (20-40%)
One phenotype	Blue bloater and pink puffer	Multiple asthma and COPD phenotypes have now been identified

Immunology of Asthma and COPD: Traditional View



Inflammatory Cells/ Mediators
Asthma vs. COPD – The Tradional View

Asthma

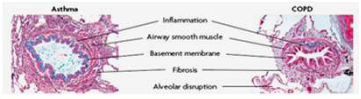
- Eosinophils and mast cells
- Neutrophils (severe)
- CD 4+ T_H2 cells
- LTC4, D4, E4
- Cytokines
  - IL 4, IL 5, IL 13
  - RANTES, eotaxins, MCP-1

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

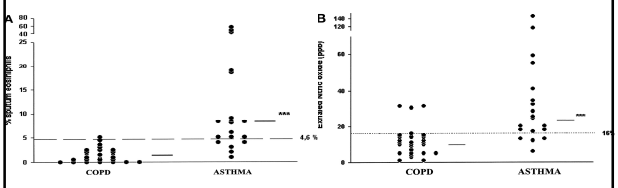
Pathology of Asthma and COPD



Inflammation	+++	+++
Airway smooth muscle	+++	+
Basement membrane	++	–
Fibrosis	+ (subepithelial)	+++ (peribronchiolar)
Alveolar disruption	–	+++
Airway vessels	++	No change
Mast cells	++ (and activated)	Normal
Dendritic cells	++	ND
Eosinophils	++	Normal
Neutrophils	Normal	++
Lymphocytes	T_H2 type	T_H1 and T_C1 type
Epithelium	Often shed	Pseudostratified
Goblet cells	++	++

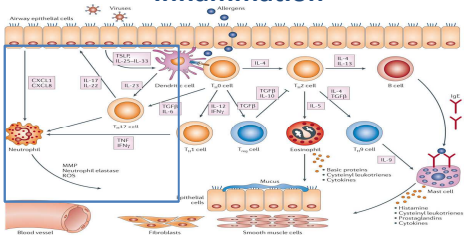
Nature Reviews 2008;8:183-192

Airway Inflammation Biomarkers
Asthma vs. COPD



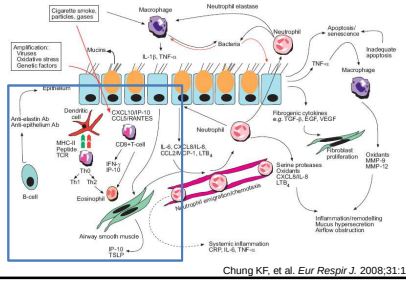
Fabbri LM et al Am J Respir Crit Care Med 2003;167 418-424

Pathobiology of Asthma: Beyond TH2-Inflammation



Pelaia G, et al. *Nature Reviews. Drug Discovery* 2012; 11: 958 - 972

Pathobiology of COPD: Beyond Neutrophilic Inflammation



Chung KF, et al. *Eur Respir J.* 2008;31:1334-56.

Inflammation- Similarities

- Alveolar inflammation demonstrated in asthma [1]
- Severe asthma / Smokers with asthma/ Elderly Asthma- BAL with neutrophils [2]
- COPD: tissues and airway eosinophils in some patients and during exacerbations
  - Pts with eosinophils have better response to steroids [3]

[1] Kraft M.Am J Respir Crit Care.Med 1996:154:1505
[2] Wenzel S Am J Respir Crit Care Med:1999:160:1001
[3] Chanez P Am J Respir Crit Care Med 1997:155:1529

Asthma with Features of COPD

Unsuspected Loss of Lung Elastic Recoil in Chronic Persistent Asthma

Decreased Elastic sthma

Arthur F. Noe Zame

[Commentary]

CHEST

Unraveling the Pathophysiology of the Asthma-COPD Overlap Syndrome

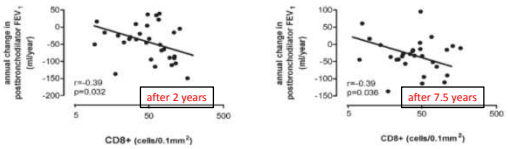
Unsuspected Mild Centrilobular Emphysema Is Responsible for Loss of Lung Elastic Recoil in Never Smokers With Asthma With Persistent Expiratory Airflow Limitation

Arthur F. Gelb, MD, FCCP; Alfred Yamamoto, MD; Eric K. Verbeken, MD; and Jay A. Nadel, MD

Bronchial CD8 Cell Infiltrate and Lung Function Decline in Asthma

Elizabeth L. J. van Rensen, Jacob K. Sont, Christine E. Evertse, Luuk N. A. Willems, Thais Mauad, Pieter S. Hiemstra, Peter J. Sterk, and the AMPUL Study Group*

Departments of Pulmonology and Medical Decision Making, Leiden University Medical Center, Leiden, The Netherlands; and Department of Pathology, Sao Paulo University Medical School, Sao Paulo, Brazil



Traditional Approach in Differentiating Asthma and COPD- Immunology/ Pathology

Asthma	COPD
Airway inflammation – Eosinophilic predominant	Airway inflammation- Neutrophilic predominant
Predominantly medium airway inflammation	Predominant small airway inflammation and parenchymal lung destruction

Traditional Approach in Differentiating Asthma and COPD- Immunology/ Pathology

Asthma	COPD	Problem with the approach
Airway inflammation – Eosinophilic predominant	Airway inflammation- Neutrophilic predominant	• The presence of inflammatory cells in the airways does not differentiate asthma from COPD but their measurement may guide treatment decisions. • Airway inflammation is heterogeneous and multiple endotypes for both have been identified
Predominantly medium airway inflammation	Predominant small airway inflammation and parenchymal lung destruction	• Airway inflammation in asthma often involve the small airway and parenchymal changes including lung destruction have been described. • Inflammation in COPD can involve multiple components of the lung as well can be associated with systemic inflammation

Physiologic Differences: Traditional View

Asthma
- Reversible airway obstruction
- Normal DLCO
- Normal lung volume
- Normal elastic recoil (except in severe disease)
- Flow dominant BD response
- BHR almost always present

COPD
- Partially reversible obstruction
- Abnormal DLCO
- Hyperinflation
- Decreased elastic recoil
- Volume dominant BD response
- BHR only in some patients

Sciurba FC, CHEST 2004;117S-124S
Gelb AF, Curr Opin Pulm Med 2008; 14: 24 - 30

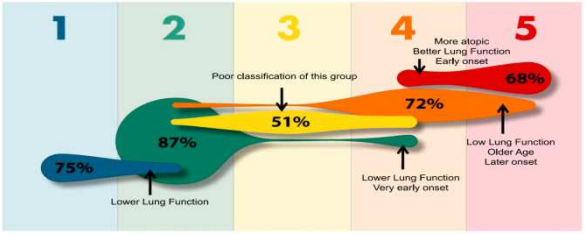
Boulet L Can Respir J 1998:5:270
Fabbri LM Am J Respir Crit Care Med 2003:167:418
Magnussen H. Clin Exp Allergy 1998 28:187

Clinical Heterogeneity in the Severe Asthma Research Program

Wendy C. Moore[1], Anne M. Fitzpatrick[2], Xingnan Li[1], Annette T. Hastie[1], Huashi Li[1], Deborah A. Meyers[1], and Eugene R. Bleecker[1]

[1]Wake Forest University School of Medicine, Center for Human Genomics, Winston Salem, North Carolina; and [2]Emory University School of Medicine, Atlanta, Georgia

Ann Am Thorac Soc Vol 10, Supplement, pp S118-S124, Dec 2013

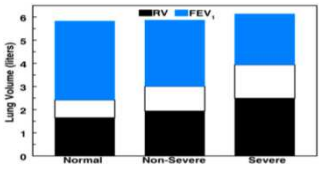


Severe Asthma

Lessons Learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program

Nizar N. Jarjour[1], Serpil C. Erzurum[2], Eugene R. Bleecker[3], William J. Calhoun[4], Mario Castro[5], Suzy A. A. Comhair[2], Kian Fan Chung[6], Douglas Curran-Everett[7], Raed A. Dweik[2], Sean B. Fain[1], Anne M. Fitzpatrick[8], Benjamin M. Gaston[9], Elliot Israel[10], Annette Hastie[3], Eric A. Hoffman[11], Fernando Holguin[12], Bruce D. Levy[10], Deborah A. Meyers[3], Wendy C. Moore[3], Stephen P. Peters[3], Ronald L. Sorkness[1], W. Gerald Teague[9], Sally E. Wenzel[12], and William W. Busse[1]; for the NHLBI Severe Asthma Research Program (SARP)*

Am J Respir Crit Care Med Vol 185, Iss. 4, pp 356–362, Feb 15, 2012

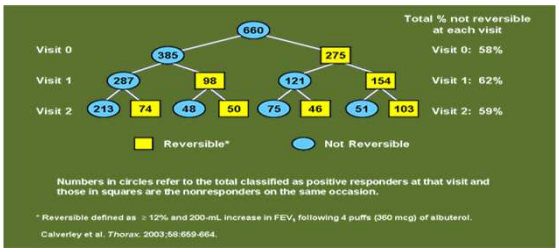


Residual Volumes ↑

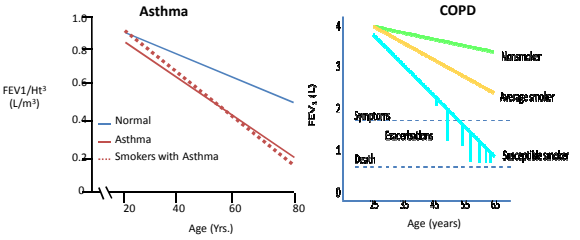
air trapping?

emphysema?

Acute Bronchodilator Response Does not Differentiate Between Asthma and COPD



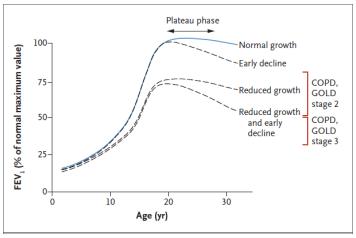
Lung Function Decline: Asthma vs. COPD



Peat JK. Eur J Respir Dis. 1987

Mannino DM. *Chest.* 2002;121:121S-126S. Fletcher and Peto, 1977

Longitudinal Lung-Function Trajectories in Asthma



Factors associated with reduced lung growth:

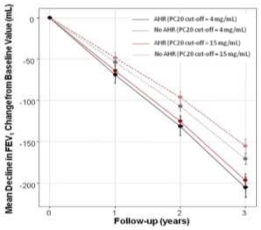
- **Lower baseline FEV1**
- **Smaller bronchodilator response**
- **AHR at baseline**
- **Male sex**

M.J. McGeachie et al. *N Engl J Med* 2016;374:1842-52.

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



Tkacova R et al. J Allergy Clin Immunol 2016

Traditional Approach in Differentiating Asthma and COPD- Physiology

Asthma	COPD
Reversible airway obstruction	Only partially reversible airflow obstruction
Normal DLCO Normal lung volumes	Low DLCO (emphysema) Hyperinflation and gas trapping
Airway hyperresponsiveness (AHR)	No airway hyperresponsiveness (AHR)
Lung function decline	Lung function decline

Traditional Approach in Differentiating Asthma and COPD- Physiology

Asthma	COPD	Problem with the approach
Reversible airway obstruction	Only partially reversible airflow obstruction	A subgroup of patients with long standing asthma do not demonstrate reversible airflow obstruction. Acute bronchodilator reversibility are common features of COPD
Normal DLCO Normal lung volumes	Low DLCO (emphysema) Hyperinflation and gas trapping	Some patients with severe asthma have physiologic abnormalities seen in COPD (Increase RV/TLC, low DLCO)
Airway hyperresponsiveness (AHR)	No airway hyperresponsiveness (AHR)	Some patients with asthma fail to demonstrate AHR, 60% of COPD patients have AHR (correlate with poor outcomes)
Lung function decline	Lung function decline	In a subgroup of asthma, lung function decline may result in airway obstruction that resembles COPD

Similar Goals of Management

Treatment Guidelines

GINA **GOLD**

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

GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Medications for Asthma and COPD

Asthma

Anti-inflammatory drugs
- Corticosteroids
- Antileukotrienes
- Theophylline (?)

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

ICS/LABA combination
Anti IgE
Anti IL-5

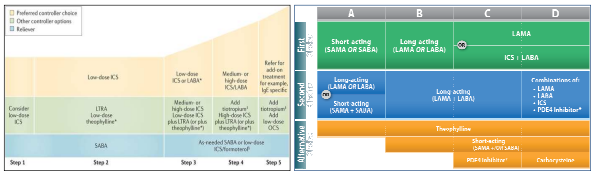
COPD

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

Anti-inflammatory drugs
- Corticosteroids
- PDE4 Inhibitor (Roflumilast)

ICS/LABA Combination
Mucoactive drugs
Antibiotics
Vaccination

Asthma and COPD Pharmacological Treatment Options: Current Guidelines



Holgate ST, et al. Nat Rev Dis Primers. 2015;1:15025.

Adapted from: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

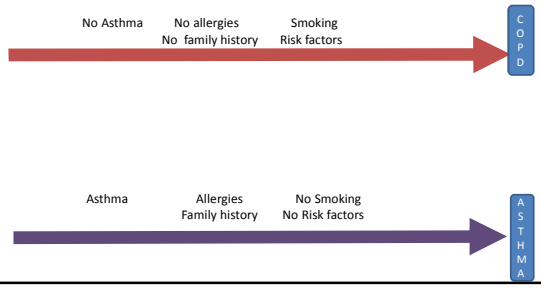
Traditional Approach in Differentiating Asthma and COPD- Response to Therapy

Asthma	COPD
Steroid-responsive	Relative steroid resistant
Marked response to bronchodilators	Partial response to bronchodilators
LABA monotherapy unsafe	LABA monotherapy safe

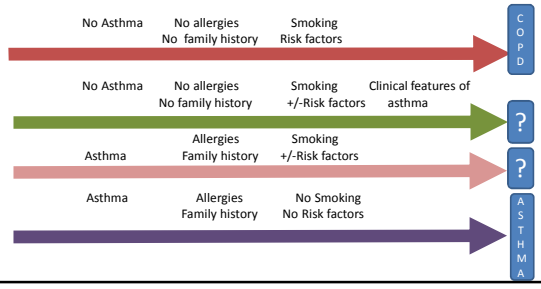
Traditional Approach in Differentiating Asthma and COPD- Response to Therapy

Asthma	COPD	Problem with the approach
Steroid-responsive	Relative steroid resistant	• A moderate prportion of COPD patients have eosinophilic airway inflammation which predict response to inhaled steroids. • Asthma patients with Low T2 airway inflammation or no inflammation do not respond to steroids
Marked response to bronchodilators	Partial response to bronchodilators	• Variable according to disease severity and duration. • COPD patient demonstrate volume response
LABA monotherapy unsafe	LABA monotherapy safe	• Some patients with COPD have asthma component

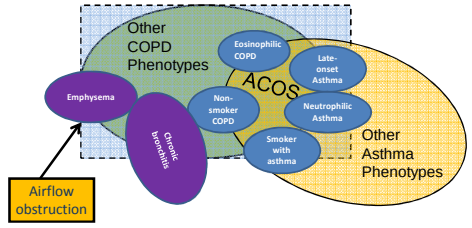
Pathways to Chronic Airflow Obstruction



Pathways to Chronic Airflow Obstruction



The Overlap Between Asthma and COPD Emerging View: Is this ACOS??



ERJ Express. Published on June 23, 2016 as doi: 10.1183/13993003.00436-2016

PERSPECTIVE
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Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and Asthma - COPD Overlap Syndrome (ACOS)

What is asthma–COPD overlap syndrome? Towards a consensus definition from a round table discussion

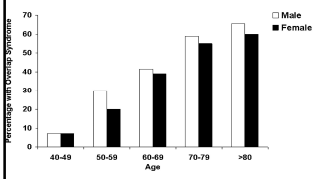
Don D. Sin[1], Marc Miravitlles[2], David M. Mannino[3], Joan B. Soriano[4], David Price[5,6], Bartolome R. Celli[7], Janice M. Leung[1], Yasutaka Nakano[8], Hye Yun Park[9], Peter A. Wark[10] and Michael E. Wechsler[11]

TABLE 1 Criteria for diagnosis of asthma–chronic obstructive pulmonary disease overlap syndrome

Major	Minor
1. Persistent airflow limitation (post-bronchodilator FEV_1/FVC <0.70 or LLN) in individuals 40 years of age or older; LLN is preferred	1. Documented history of atopy or allergic rhinitis
2. At least 10 pack-years of tobacco smoking OR equivalent indoor or outdoor air pollution exposure [*e.g.* biomass]	2. BDR of FEV_1 ≥200 mL and 12% from baseline values on 2 or more visits
3. Documented history of asthma before 40 years of age OR BDR of >400 mL in FEV_1	3. Peripheral blood eosinophil count of ≥300 cells·uL^{-1}

The committee recommends presence of all three major criteria and at least one minor criterion for asthma–chronic obstrucvie pulmonary disease overlap syndrome. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BDR: bronchodilator response using 400 ug of albuterol/salbutamol [or equivalent]; LLN: lower limit of normal.

Prevalence of Overlap Syndrome Increases with Age



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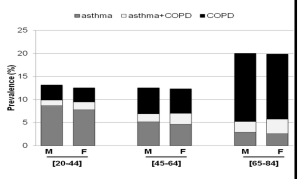


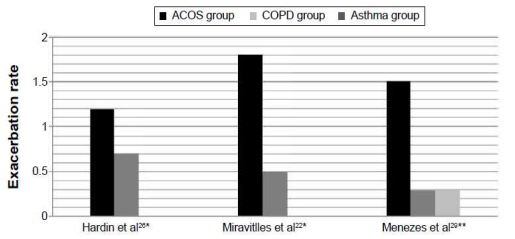
de Marco R et al. PLoS ONE 2013: 8: e62985

What do we know about ACOS?

Measure	Asthma	ACOS	COPD
Symptoms	Intermittent, worse at night or in the morning	Progressively worsen	Progressively worsen
FEV_1/FVC	≥70%	<70%	<70%
FEV_1 %predicted*	>80%	<80%	<80%
AHR, PD_{15}^	<12 ml	<12 ml	>12 ml
PB increase in FEV_1	≥12% and 400 ml (marked reversibility)	≥12% and ≥200 ml (reversible)	≥12% and ≥200 ml (reversible)
FeNO	>50 ppb	25–50 ppb	<25 ppb
DLco	Normal, although smokers may present with a lower DLco	Normal–low	<80% predicted
Imaging	Usually normal	Bronchial wall thickening, emphysema, gas trapping on expiratory chest CT scans, greater segmental wall area on inspiratory CT scans, fibrosis, hyperinflation	Bronchial wall thickening, emphysema, fibrosis, hyperinflation
Inflammation	Eosinophils > neutrophils, mast cells, CD4+ T lymphocytes IgE, IL-4/-5/-13, eotaxin	Eosinophils and neutrophils, CD4+ and CD8+ T lymphocytes IgE, IL-4/-5/-13/-1β/-8/-6, TNF-α, eotaxin, proteases	Neutrophils > eosinophils, CD4+, CD8+ T lymphocytes IL-1β/-8/-6, TNF-α, proteases
Test for atopy, (MAST)	Commonly allergic to environmental allergens	Commonly allergic to environmental allergens	Do not rule out COPD, ACOS may be more likely
Exacerbations	>3/year, well controlled by treatment	More frequent than asthma and COPD alone	>2/year

B. Ding & A Enstone. Expert Rev Respir Med 2016; 10:3, 363-371,

Exacerbation Rate in Patients with ACOS



International Journal of COPD 2015:10 1443–1454

Moving from the Oslerian Paradigm to Post-genomic Era: Are Asthma and COPD Outdated Terms?

- Complex interaction between genetic predisposition and the environment
- Inflammation plays a key role for both, neutrophilic and eosinophilic inflammation can be seen in both
- Heterogeneous (variable) natural history & clinical course
- Airway obstruction and hyperresponsiveness underly pathophysiology and is associated with progressive loss of lung function
- The presence or absence of reversibility of FEV1 does not distinguish one from the other
- Approach to management for both involves risk factor modifications, self management education and pharmacotherapy