



Asthma and COPD: 2010

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Disclosures/Conflict of Interest

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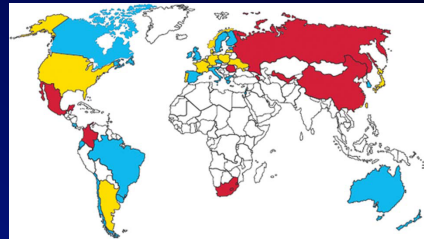
Speakers Bureau: Merck, Beringer-Ingelheim, Pfizer



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Trends of Asthma Morbidity/ Mortality

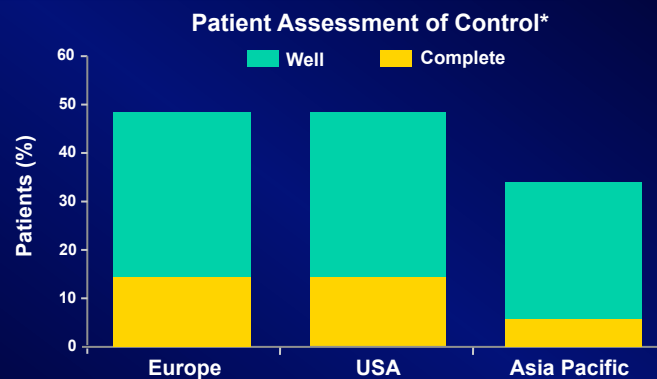
- Each day in the United States
 - 63,000 people miss work and school
 - 34,000 have an asthma attack
 - 5,000 people visit the Emergency Room
 - **Because of Uncontrolled Asthma**
- About 15 people die daily
 - Many young, healthy
 - Should be considered preventable



- Asthma deaths per 100,000 population age 5-34
- Red > 10
- Yellow 5-10
- Blue < 5

Papirus, Drugs 2009; 69 (17):2366-87

Patient Assessment of Control



*Patients with severe persistent symptoms –past 4 weeks: symptoms ≥ 3 times per day in the daytime; most nights/every night.

Rabe KF, et al. *Eur Respir J*. 2000;16(5):802-807. National Survey Data.
Lai CKW, et al. *J Allergy Clin Immunol*. 2003;111:263-268.

Prevalence of Uncontrolled Asthma

- Real-world Evaluation of Asthma Control and Treatment (REACT)
 - 55% (Web based using ACT)
- Epidemiologic Study on Genetics of Asthma
 - 38% of patients using ICS
- Claims data study (Stempel et al)
 - 40% using claims data

Factors Contributing to Uncontrolled Asthma

- Physician
 - Underestimate severity /undertreatment
 - No self-management teaching/no action plan
- Patient
 - Non-adherence with controller therapy
 - Failure/delay in detecting early warning signals
 - Failure/delay in implementing an action plan
- Health System
 - Lack access to care
 - Inability to afford medication
- Disease specific
 - Unremitting trigger (cat, tobacco, occupational exposure)
 - Difficult-to-treat asthma

Asthma 2010

- What have we learned about the types of asthma?

Inflammatory Response in Asthma

➤ Key Cells

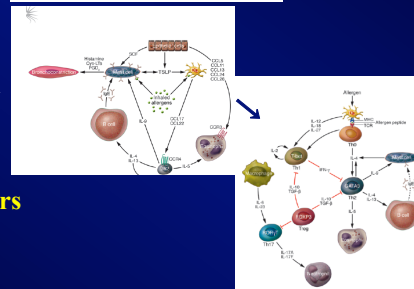
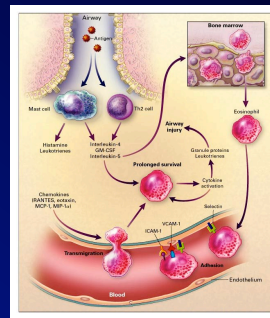
- Dendritic cells
- T lymphocytes (CD4+)
- Eosinophils
- **Mast cells** (TNF α ; IL-8)
- **Neutrophils**

➤ Genetic Predisposition

- Population – 4 to 8 %
- First degree relative – 25%
- Gene: Environmental timing critical (bacteria in airway at one month)

➤ Asthma 2010 more complex

- NIH study: **5 separate asthma clusters**
- Severe asthma: PMNs; Mast cells



Identification of Asthma Phenotypes

- Severe Asthma Research Program (www.atsjournals.org)
 - Enrolled 750 asthmatics (mild to severe)
 - 628 variables: 34 core variables
- Cluster analysis found 5 distinct subtypes:
 - **Cluster 1** (15%): atopic; normal lung function (LF)
 - **Cluster 2** (45%): atopic; near normal LF = 2-3 meds
 - **Cluster 3** (10%): obese females; freq oral steroids/ HCU
 - **Cluster 4/5** (30%): reduced LF (FEV_1); high HCU
 - **Cluster 4**: atopic; F/M=1; childhood onset; could normalize LF
 - **Cluster 5**: non-atopic; F/M >1; $FEV_1 < 80\%$ (after 8 puffs albuterol)
- Future studies: evaluate subset responses to therapy

Inhaled Corticosteroids (ICS)



Fluticasone
Flovent®



Beclomethasone
QVAR®



Ciclesonide
Alvesco®



Budesonide
Pulmicort®



Mometasone
Asmanex®

Selecting and dosing ICS

- 5 RCTs compared 3 ICS (Beclomethasone, Budesonide, Fluticasone) at low dose (200–400 BDP ug/d or equivalent)
- 7 RCTs compared them at high doses (800–2000 ug BDP/d or equivalent)
- “No major differences at the clinically accepted equivalent doses”
- **2010: Emerging data that delivery to small airways important in severe asthma**

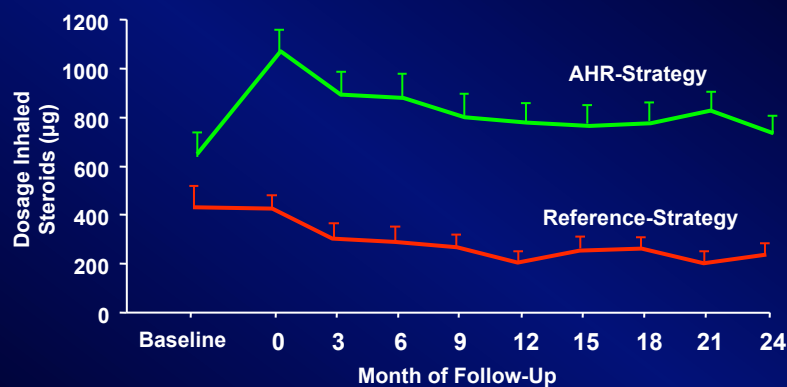
Main Health Technology Assessment 2008 (British National Health Service)

How Do We Assess Control ?

Utility of AHR in Asthma

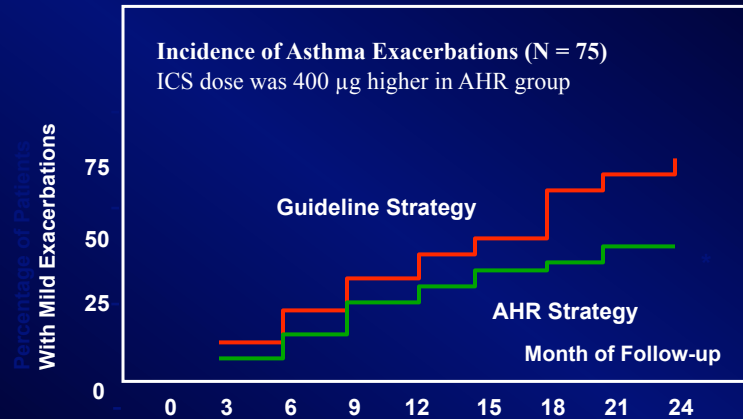
- **Advantages**
 - Asthma severity is related to the severity of AHR
 - AHR is diagnostic tool for asthma
- **Limitations**
 - AHR can be abnormal even in the absence of asthma symptoms or when lung function is normal
 - Baseline FEV_1 <60% of predicted or <1.5 L is a relative contraindication to performing BHR

AHR for Asthma Control



Sont JK, et al. *Am J Respir Crit Care Med*. 1999;159:1043-1051

Control of AHR: Mild Exacerbations



* 1.8-fold decrease in exacerbation rate vs guideline strategy ($P=0.03$).
Mild exacerbations = increase of ≥ 3 points in total asthma score.

Sont JK, et al. *Am J Respir Crit Care Med*. 1999;159:1043-1051.

2010: Studies on inhaled mannitol to assess AHR

Surrogates of Inflammation: FE_{NO}

- An **evolving biomarker** increasingly being used in clinical practice
- May be useful to rule out a diagnosis of asthma in patients presenting with dyspnea
- Increased concentrations may be associated with insufficient asthma control
- May be useful to guide therapy and assess adherence with ICS

Smith AD et al. *N Engl J Med*. 2005;352:2163-2173.

Utility of eNO as Biomarker

- **Advantages**
 - Reliable, noninvasive, and easily measured
 - Positive predictive value for loss of asthma control is 80% - 90%¹
 - Response of eNO to ICS was dose dependent and reproducible²
- **Limitations**
 - Also increased in bronchiectasis and viral infections³
 - Several factors can affect eNO measurements - smoking, spirometry, sputum induction, and alcohol³
 - Wide range of eNO levels in patients with asthma³
 - eNO levels are often normal in ICS-treated patients

Components of Severity		Classification of Asthma Control (Youths ≥12 years of age & adults)		
		Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2/month	1-3/month	≥4/week
	Short-acting β_2 -agonist use for symptom control	≤2 days/week	>2 days/week	Several times per day
	Interference with normal activity	None	Some limitation	Extremely limited
	FEV ₁ or peak flow	>80% pred/personal best	60-80% pred/personal best	<60% pred/personal best
	Validated questionnaires			
	ATAQ	0	1-2	3-4
	ACQ	≤0.75	≥1.5	N/A
	ACT	≥20	16-19	≤15
Risk	Exacerbations	0-1 per year	2-per year	>2 per year
	Reduction in lung growth	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects vary in intensity from none to very troublesome. Level of intensity does not correlate to specific levels of control but should be considered in overall assessment of risk.		

Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home? Score

All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	<input type="text"/>
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2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	<input type="text"/>
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3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?

4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	<input type="text"/>
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4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	<input type="text"/>
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5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	<input type="text"/>
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Points Total

Score < 20: Best predictor of exacerbation

The LABA controversy-a quick review

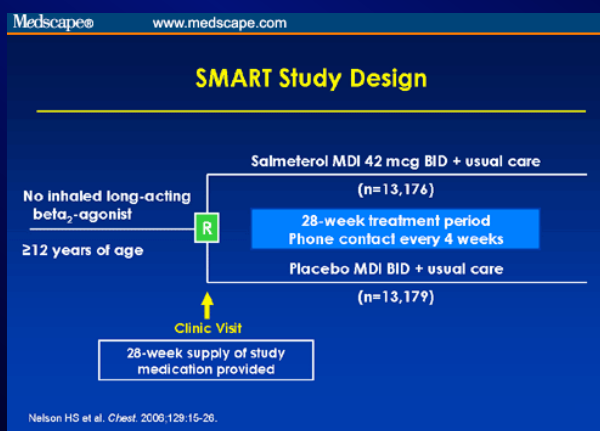
Long acting beta agonists (LABAs) and fixed dose ICS/LABA



Formoterol

Salmeterol
Serevent®Fluticasone and Salmeterol
Advair®Budesonide and
Formoterol
Symbicort®

Salmeterol Multicenter Research Study (SMART)



Nelson et al Chest 2006

- Increase in respiratory and asthma related deaths and life threatening experiences particularly in African- Americans
- "Usual asthma care" often deviated from asthma guidelines
- Only 47% of all patients were prescribed ICS, (49% of Caucasians, and 39% of African-Americans)

FDA meta-analysis 2008

<u>Trials</u>	<u>LABA</u>	<u>No LABA</u>	<u>Risk difference (RD) 95 % CI</u>
<u>Risk differences for specific and composite outcomes</u>			
Asthma death	16/30,148	4/30,806	0.4 (.11-.69)
Death or intubation	44/30,148	27/30,806	0.57 (0.01-1.12)
Hospitalization	369/30,148	399/30,806	2.57 (0.9-4.23)
Composite outcome (death, intubation, hospitalization)	381/30,148	304/30,806	2.80 (1.11-4.49)
<u>Composite outcome stratified by use or nonuse of randomized mandatory ICS</u>			
LABA w/o randomized ICS vs. no LABA	350/22,286	279/24,474	3.63 (1.51-5.75)
LABA with randomized ICS vs. randomized ICS	31/7,862	26/7,330	0.25 (-1.69-2.18)

Where are we.....

- LABA monotherapy for asthma is clearly harmful*
- Use of ICS with LABA reduces but may not completely eliminate possible risk (Levenson 2008, Weatherall 2010)
- No clear evidence risk to date with fixed dose combination ICS/LABA but studies and meta-analyses are underpowered to definitively exclude risk
- LABAs should preferentially be used in fixed dose combination in patients not controlled with low/moderate dose ICS alone
- *Yet 7-11% PCPs use LABA alone for asthma

Stepdown: guidelines and the 2010 FDA recommendations for safe LABA use

- FDA recommends that LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved
- EPR3 does not make a specific recommendation regarding stepdown from ICS/LABA
- Studies suggest that initial LABA stepdown (same ICS) can lead to loss of control; some existing studies support stepdown of ICS first and d/c of LABA if low dose ICS can be achieved
 - Lemanske 2001
 - Fowler 2002
 - Bateman 2006
 - Godard 2008
 - Reddel 2010
 - Hagiwara 2010

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 18, 2010 VOL. 362 NO. 12

Step-up Therapy for Children with Uncontrolled Asthma
Receiving Inhaled Corticosteroids

- Childhood asthma \neq adult asthma; lower response to LABA
- Adding LABA was more likely to be the best treatment; but many children responded better to others treatments (LTRA or increasing ICS)
- **Key clinical message:** monitor pt. response to treatment, if it doesn't work, try others within that step before moving to a higher step.

Asthma 2010

- **Who is at risk for severe exacerbation of asthma?**

Risk Factors for Severe/Fatal Asthma

- Equal among mild, moderate, and severe asthma*
- Key risk factors:
 - Ever been intubated or in ICU for asthma
 - Hospitalized in last year
 - Deficiency in self-management skills
- Predictors of health care utilization:
 - Score of < 20 on Asthma Control Test (ACT)
 - **Poor perception of dyspnea**

*Clin & Exper Allergy 2007; 37:552-557

Factors Influencing the Heterogeneity of Asthma Control: Poor Perception of Dyspnea (POD)

113 Asthmatics Evaluated

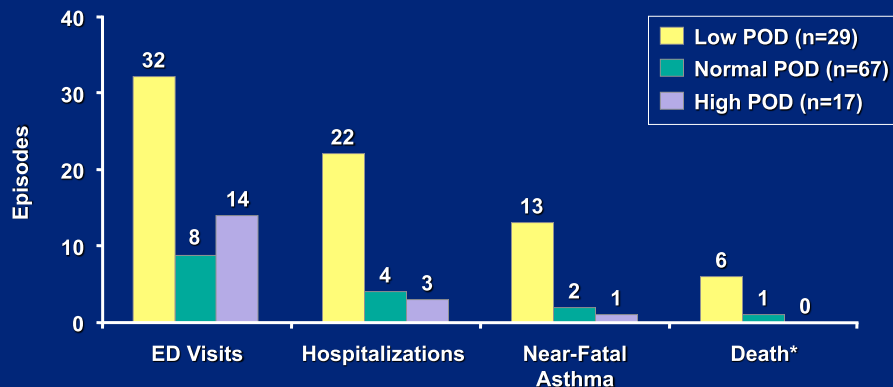
- Breathe against 2-way valve load of 0-, 5-, 10-, 20-, and 30-cm H₂O for 1 minute
- Dyspnea defined as modified Borg scale
- POD
 - Low 29 (26%)
 - Normal 67 (59%)
 - High 17 (15%)

*Puffs/day.

Magadle R et al. *Chest*. 2002;121:329-333.

- β_2 -Agonist use in 4 weeks*
 - Low 1.7/day
 - Normal 2.4/day
 - High 4.1/day
- Patients with asthma and a low POD had tendency toward
 - Older age
 - More females
 - Longer duration
 - More severe
- Documented events over 2 years

Poor Perception of Dyspnea (POD)



*Of deaths in the low POD group, 4 were asthma related, 2 were unknown.

Multiple studies now that show underperceivers and life-threatening asthma may have a 20% mortality from asthma

ASTHMA 2010

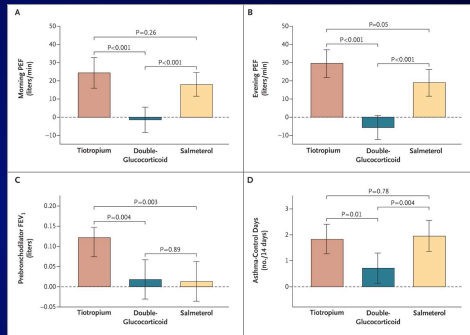
- Review of new concepts ?

Update in Asthma 2010

- Large RCT showed routine use of PPI not beneficial (NB: subjects without GERD sx's)
- Fungal Asthma Sensitization Trial (FAST)
 - Itra beneficial: severe asthma with + fungal skin test
- MIA study: "Macrolides in Asthma"
 - Found low incidence of Mycoplasma
 - Macrolides not beneficial in mild asthma
- Anti -IL-5 therapy in severe asthma
 - Early study showed anti-IL5 of no benefit
 - Two studies: large difference in exacerbations
- Low Vitamin D levels: worse immunologic dz.

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

- TALC study
 - Poorly controlled on ICS
 - Double ICS
 - LABA (salmeterol)
 - LAMA (Tio)
- Primary endpoint
 - PEFR
- Secondary
 - FEV₁
 - Asthma control days
- No long term data



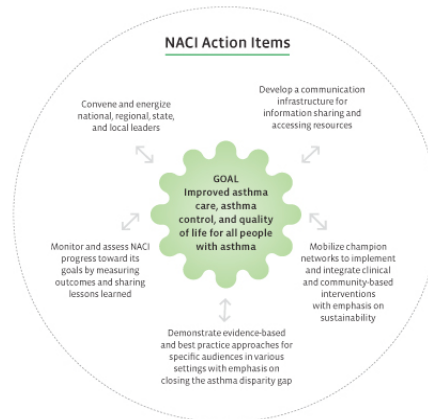
N Engl J Med 2010;363:1715-26
October 28,2010

ASTHMA 2010

- What can we do to improve the care of patients with asthma?

The NACI Plan of Action

1. Convene and energize national, regional, state, and local leaders
2. Develop communication infrastructure
3. Mobilize "asthma champion networks"
4. Demonstrate evidence-based interventions for specific audiences
5. Monitor and assess NACI progress



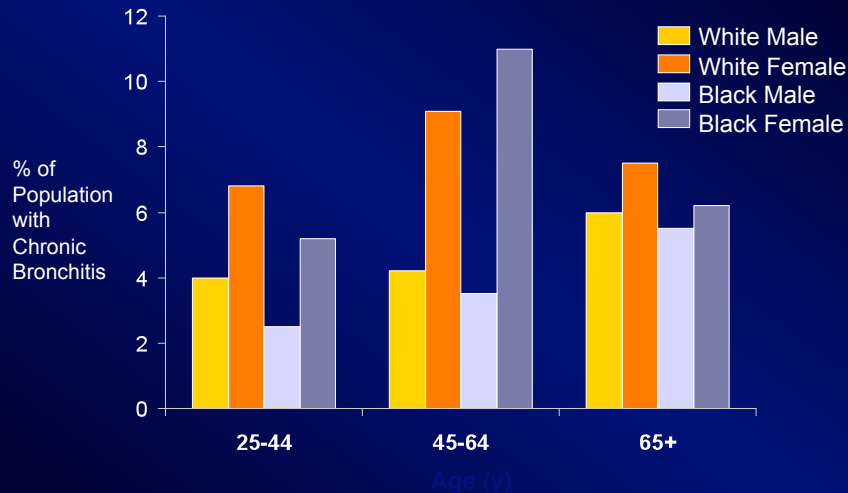
National Asthma Control Initiative

NACI Web site: <http://naci.nhlbi.nih.gov>

COPD 2010

- What have we learned about COPD?

Shifting Patient Profile in COPD: 2010

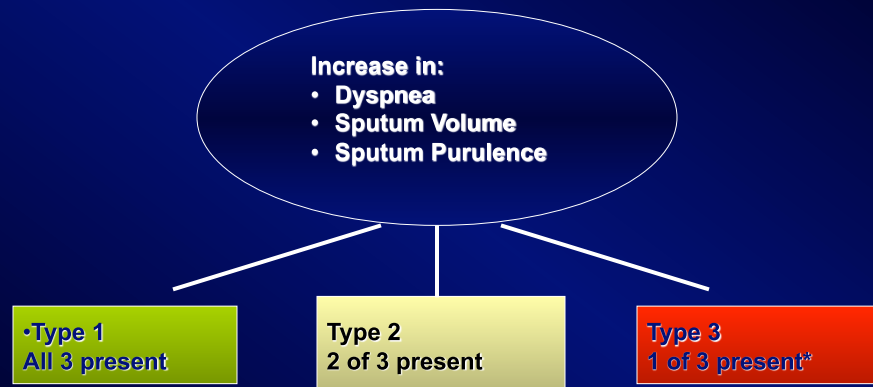


NHLBI. *COPD Data Fact Sheet*. Available at: www.nhlbi.nih.gov/health/public/lung/other/copd_fact.pdf.

Basics of Treating COPD: 2010

- Initiation of long-acting bronchodilator
 - Canadian guidelines suggest cost-effective to start with a LABA (salmeterol/formoterol) or LAMA (tiotropium)
 - Less exacerbations & better quality of life
 - Much better compliance
 - Inhaled Corticosteroids: Risk vs. Benefit
 - Risk: Increase risk of pneumonia with RR= 1.6
 - Benefit: FEV₁ < 50 % or "asthma/atopic" features with eosinophils, frequent exacerbations, or positive BD test
 - Home oxygen
 - Saturation $\leq 88\%$ (or $\leq 89\%$ with Cor Pulmonale)
 - Must wear oxygen 15 hours/day for survival benefit

Patient Stratification by Exacerbation Characteristics

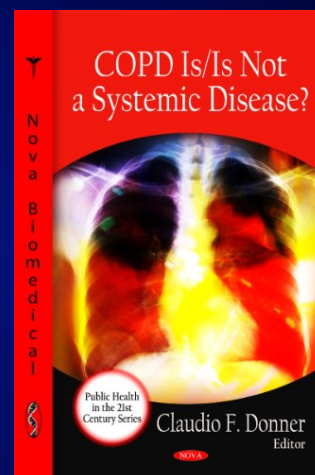


Anthonisen et al. *Ann Intern Med* 1987;106:196

- Type 1 significant benefit from antibiotics; Type 2 borderline benefit
- Procalcitonin: < .1 ug/L no infection; > .25 ug/L antibiotics

New Concepts in COPD

- Is COPD a systemic disease?
- What screening tools are needed?
- Multiple co-morbidities of COPD:
 - Osteoporosis
 - Congestive heart failure
 - Anxiety/depression
 - Cachexia/muscle wasting



New Concepts in COPD

- COPD as a systemic inflammatory disease
 - Inflammation in lung spills over into the blood
 - Smoking or hypoxemia causes inflammation
 - Inflammation in skeletal muscles
- Observations
 - FEV₁ closely linked with CAD/hypertension
 - Elevated CRP (NHANES 3: closely linked to COPD)
 - TNF-alpha, IL-6, IL-8 all elevated
 - Sns of oxidative stress ↑ in muscles in severe COPD

Evaluation/Treatment of Co-morbidities

- Osteoporosis
 - DEXA scan in GOLD stage III-IV
 - Calcium, vitamin D, biphosphanates
- Major depression (severe COPD)
 - Ranges from 19-42%; Referral when indicated
- Malnutrition/mucle wasting
 - Significant risk factor hospitalization/mortality
 - BMI ≤ 21 : REE 20% above normals; +/- effect Rx
- CHF: common cause of increase dyspnea
 - BNP: good discriminator
 - Primary Rx: cardio-selective beta-blockers; safe in COPD

COPD 2010

- What is the role of pulmonary rehab in COPD?

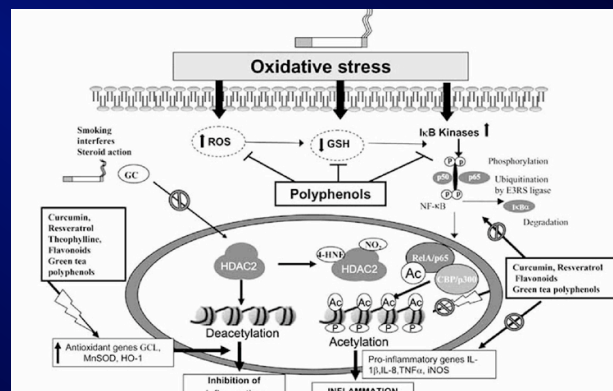
Pulmonary Rehab in COPD

- Pulmonary Rehab Programs (12 weeks):
 - Reduce dyspnea and improve quality of life
 - Increase exercise tolerance
 - Show a trend toward reduced health care costs
- Only 1-2% of COPD pts. receive rehab
- Canadian multicenter RCT on Home Rehab (n=252)
 - Home Based vs. Hospital Based program (1 yr study)
 - No difference in QOL, dyspnea score at 3 & 12 months
 - No serious adverse events

Maltias et. al. Ann Intern Med 2008;149:869-878
Thorax 2009 (7):619

What is the story about cigarette smoke?

Corticosteroids and Tobacco Smoke

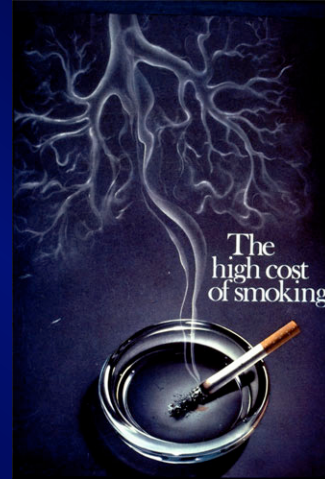


- Tobacco smoke inactivates histone deacetylases
- Up to 25% of asthmatics smoke and 30% of children are exposed to ETS; 95% COPD smoke related
- Dramatically reduces the effects of ICS

Barnes et. al. Eur Respir J 2009; 33: 1010–1017

The Key to Treating COPD: Smoking Cessation

- **Smoking cessation** (Lung Health Study)
 - Reduced all cause mortality (MI/ Cancer)
 - Only therapy proven to prevent ↓ FEV₁
 - Average smoker quits 5 times prior to success
- **Pharmacotherapy** (> 25% success)
 - Nicotine replacement/bupropion
 - Nicotine receptor blockade
- **Concept of the "Golden moment"**



Update on Asthma & COPD:

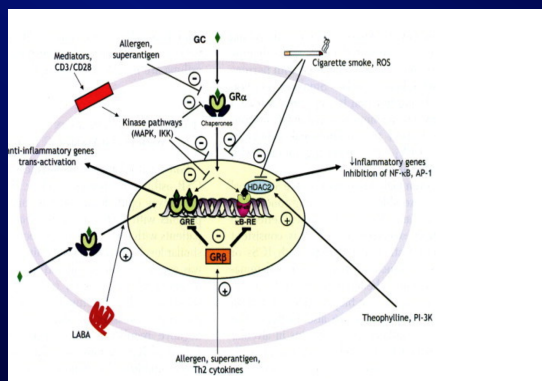


- Establish the diagnosis - requires spirometry
- Initiate long-acting bronchodilators for persisting symptoms (dual therapy for severe COPD)
- Add ICS when FEV₁ ≤ 50% & exacerbations
- Treat exacerbations with short term oral corticosteroids
- Oxygen therapy (≥ 15 hr) - saturations of 88% or less

Alternate controller medications



Responsiveness, or why ICS don't completely control everyone..



➤ Approximately 30% of patients do not achieve adequate control despite high dose ICS/LABA

➤ Mechanisms of poor response to ICS^{1,2}

- ✧ Altered molecular response to steroids
- ✧ Steroid unresponsive neutrophilic airway inflammation
- ✧ Tobacco use
- ✧ Airway remodeling

1 Adcock Curr Allergy Asthma Rep 2008
2 Lazarus Am J Respir Crit Care Med 2007

Assessing Asthma Control

- Real-world Evaluation of Asthma Control/Treatment
 - Web-based: 1812 asthmatics x 1yr
 - Matched demographics of U.S. population
 - Over ½ LABA/ICS; 85% access to care (PMD)
- ACT < 20 best predictor of asthma control
 - Unscheduled visits >2 : 12% vs 31%
 - ED visits: 10% vs 36%
 - Hospitalizations: 3% vs 14%

Every clinic visit for asthma: Asthma Control Test should be completed with vital signs

Goal ≥ 20

Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school, or at home?

Score:

2. During the past 4 weeks, how often have you had shortness of breath?

Score:

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night, or earlier than usual in the morning?

Score:

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

Score:

5. How would you rate your asthma control during the past 4 weeks?

Score:

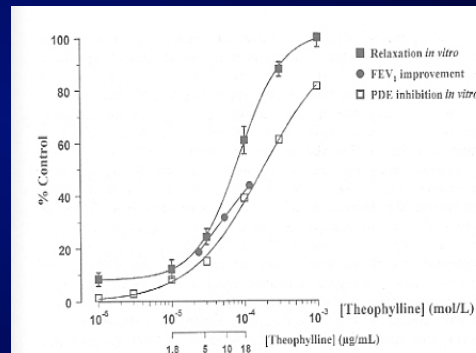
Well controlled ≥ 20 ; 16-19 not well controlled; ≤ 15 very poorly controlled
Available at: <http://www.asthmacontrol.com>

Patient Total Score:

Peters et al: J Allergy Clin Immunol 2007;119(6),1454-61

Theophylline: A Forgotten Drug

- Anti-inflammatory effect and weak bronchodilator
- Spain: add to LABA/LAMA prior to ICS if no BD response or atopic history
- Barnes (Eur Respir J 2009; 33:1010-1017)
 - Theo + ICS in smokers with asthma vs. ICS or Theo alone
 - Reduced symptoms (ACQ); improved PEFR ($p < 0.05$)
 - Increased HDAC levels in macrophages in COPD
- Conclusion:** Consider Theo/ICS in severe asthma and COPD

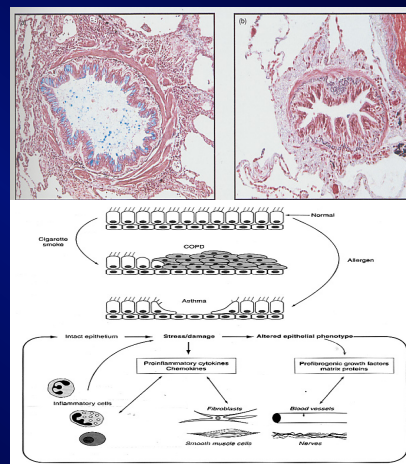


Summary of results of FDA meta-analysis 2008

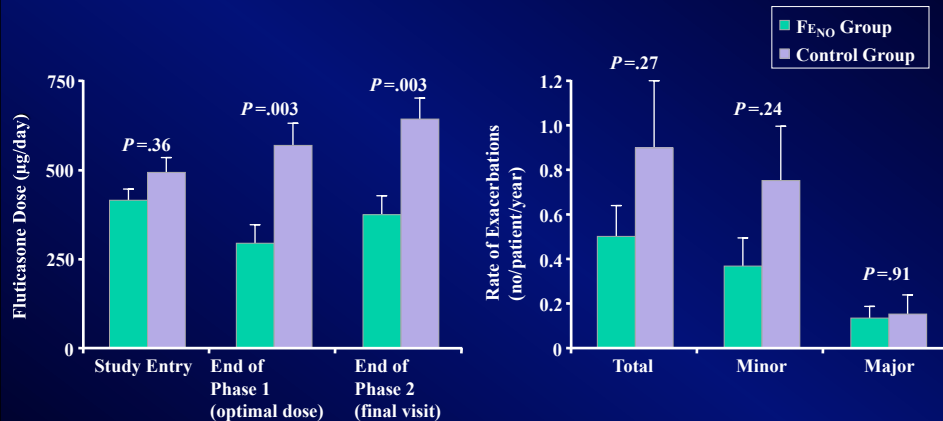
- LABAs associated with an increased risk of an asthma composite endpoint (hospitalization, intubation and death)
- 43/44 deaths and intubations in the LABA patients were in 22,286 individuals (0.19%) in trials that did not mandate the use of ICS compared with 1/7862 individuals (0.01%) in trials with mandatory ICS
- Increased risk was not apparent when LABA were used with ICS
- No deaths in either fixed dose combination groups
- Few events—limited power/cannot exclude risk

Differences in Asthma and COPD

- Not everyone who smokes gets COPD (maybe 15-20%)
- Inflammation in asthma
 - Eosinophils, Mast cells
 - Up to 30-40% Neutrophils
- Sloughing of epithelium (asthma) vs. hypertrophy (COPD)
- Physiologic differences:
 - Greater reversibility
 - **Normal DLCO** (asthma)



eNO in Asthma Therapy



Smith AD et al. *N Engl J Med.* 2005;352:2163-2173.

When patients are not responding to appropriate therapy.....

- Find out how the patient is taking medication
 - most patients use 50% of what is prescribed
- Review inhaler technique
 - Majority of patients use these incorrectly
 - Majority of MDs, RNS don't know proper use
- Tobacco use
- Persistent environmental triggers
 - Pets
 - Home environment
 - Work environment
- Medications (beta-blockers, asa/nsaids)
- Rhinosinusitis
- Severe disease
- Incorrect diagnosis

ASTHMA 2010

- Why is the environment so important to patients with asthma?

Environment

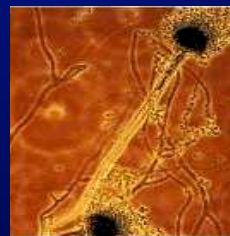
- Allergens avoidance in asthma:
 - House dust mite
 - Cat dander
 - Cockroach antigen
 - Alternaria/fungi
- Severe asthma with fungal sensitivity (SAFS)
 - Skin test/RAST for Alternaria, Penicillium, Cladosporium, and Aspergillus
 - Evaluate for mold in homes
 - Therapy with antifungals (itraconazole) may improve asthma control/QOL



Mites



Cockroach



Fungi



Cat