Optimal Assessment of Asthma Control in Clinical Practice: Is there a role for biomarkers?

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Disclosures:

- ACAAI, Immediate Past-President
- Clinical research:
  - Sunovion
  - Shionoghi
  - Genetech
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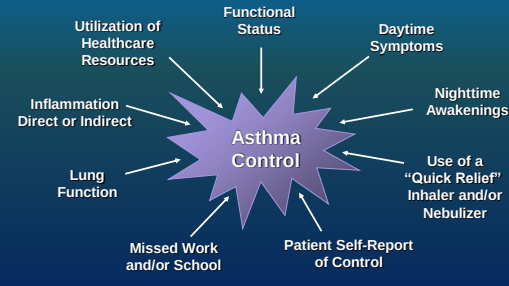
  - AstraZeneca
  - Novartis/Genetech

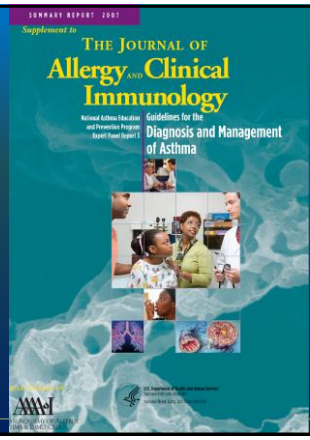
Learning Objectives

- Understand the challenges of monitoring asthma control.
- Patient perception factors complicate the measurement of control.
- Biomarkers of airway inflammation may be useful for monitoring asthma control.

How Should Control Be Measured in Asthma?



Adapted from Chipps BE, Spahn JD. *J Asthma*. 2006;43:567-572.



Goal of Asthma Therapy: Achieve Control

Reduce Impairment

- Prevent chronic and troublesome symptoms
- Require infrequent use of inhaled SABA (≤2 days/week)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels
- Meet patients' expectations of, and satisfaction with, asthma care

Reduce Risk

- Prevent recurrent exacerbations
- Minimize need for emergency department visits or hospitalizations
- Prevent progressive loss of lung function
- Provide optimal pharmacotherapy, with minimal or no adverse effects

NAEPP = National Asthma Education and Prevention Program; SABA = short-acting β_2-agonists.

Available at: http://www.nhlbi.nih.gov/guidelines/asthma/epr3/resource.pdf. Accessed February 5, 2007.

Assessing Asthma Control in Children ≥12 Years of Age and Adults: NAEPP Guidelines

Components of Control		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1-3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60%-80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75 ≥20	 1-2 ≥1.5 16-19	 3-4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year	≥2/year Consider severity and interval since last exacerbation	
	Progressive loss of lung function	Evaluation requires long-term follow-up		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		
Recommended Action for Treatment		• Maintain current step • Regular follow-ups every 1-6 months to maintain control • Consider step down if well controlled for at least 3 months	• Step up 1 step and • Reevaluate in 2 to 6 weeks • For side effects, consider alternative treatment options	• Consider short course of oral systemic corticosteroids • Step up 1-2 steps, and • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ATAQ = Asthma Therapy Assessment Questionnaire; EIB = exercise-induced bronchospasm; FEV_1 = forced expiratory volume in 1 second; NAEPP = National Asthma Education and Prevention Program.

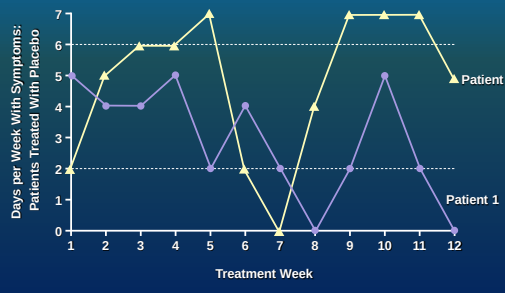
Adapted from National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3 2007). U.S. Department of Health and Human Services. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed August 29, 2007.

Challenges for the allergist: Monitoring asthma control

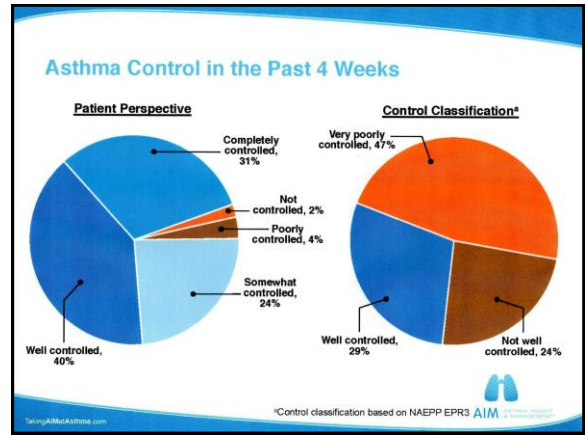
- Evaluation of asthma control is a problem
  - No single best way to monitor
  - Should be using multiple measures
- Irregularity of airway reactivity and disease activity results in both inter-patient and intra-patient variability.
- Assessment of asthma control should not be based solely on individual single time-point measures, but rather on multiple parameters.
- Patient perception of asthma control doesn't correlate with actual assessment.

. Zhang J et al. *Eur Respir J*. 2002;20:1102-1109.
Magadle R et al. *Chest*. 2002;121:329-333

Factors Complicating Measures of Control: Variability



Adapted from Calhoun W J et al. *J Allergy Clin Immunol*. 2003;112:1088-1094.



Factors Complicating Measures of Control: Poor Perception of Dyspnea (POD)

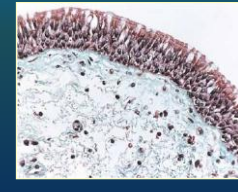
113 Asthmatics Evaluated

- Breathe against 2-way valve load of 0-, 5-, 10-, 20-, and 30-cm H_2O for 1 minute
- Dyspnea defined as modified Borg scale versus 100 controls (normal = mean ± 1 SD)
- POD
  - Low 29 (26%)
  - Normal 67 (59%)
  - High 17 (15%)
- 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

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

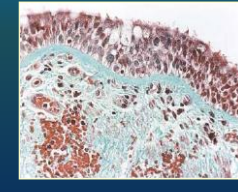
Asthma Is a Chronic Inflammatory Disease: Pathophysiologic Changes

Normal Architecture



Bronchial Mucosa From a Subject Without Asthma

Disrupted Architecture



Bronchial Mucosa From a Subject With Mild Asthma

Hematoxylin and eosin stain.
Photographs courtesy of Nizar N. Jarjour, MD, University of Wisconsin.

What Techniques Have Been Investigated to Assess Airway Inflammation in Asthma?

Technique	Considerations
Biopsy[1]	• Invasive
Airway hyperresponsiveness (AHR)[2,3]	• Time and labor intensive • Can provoke asthma exacerbation • Selection of bronchoprovocative agents (ie, methacholine, adenosine monophosphate, or mannitol)
Fraction of exhaled nitric oxide (FE_{NO})[4,5]	• Rapid • Expensive equipment • Flow-dependent technique
Sputum eosinophils[2,6]	• Tedious to perform • Test not standardized • Requires specialized lab
Exhaled breath condensate (EBC)[2-4]	• Rapid • Measurements not standardized
Eosinophilic Cationic Protein (ECP)[2]	• Detected in a variety of body fluids

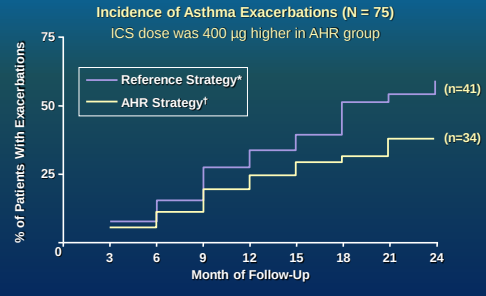
1. Vignola AM et al. *Am J Respir Crit Care Med*. 1998;157:S184-S187; 2. Menzies D et al. *J Asthma*. 2006;43:407-415; 3. National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3 2007). U.S. Department of Health and Human Services. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed August 29, 2007; 4. Baraldi E et al. *Paediatr Respir Rev*. 2006;7 (suppl):S20-S22; 5. Silkoff PE et al. ATS workshop proceedings: exhaled nitric oxide and nitric oxide oxidative metabolism in exhaled breath condensate. *Proc Am Thor Soc*. 2006;3:131-145; 6. Covar RA et al. *J Allergy Clin Immunol*. 2004;114:575-582.

Roles of AHR and Biomarkers in the Control of Asthma

- AHR[1]
  - Characteristic functional abnormality of asthma
  - Leads to variable airflow and intermittent symptoms in patients with asthma
- Sputum eosinophils[2]
  - Possibly play a role in the release of growth factors and airway remodeling
  - May be a marker for future loss of control
- FE_{NO}[3,4]
  - Elevated concentrations associated with inflammation in asthma
  - Several studies have demonstrated a relationship between asthma control and severity and FE_{NO}

1. McParland BE et al. *J Appl Physiol*. 2003;95:426-434.
2. Kay AB et al. *Trends Immunol*. 2004;25:477-482.
3. Smith AD et al. *N Engl J Med*. 2005;352:2163-2173.
4. Meyts I et al. *Ped Pulmonol*. 2003;36:283-289.

Monitoring Asthma Inflammation: AHR



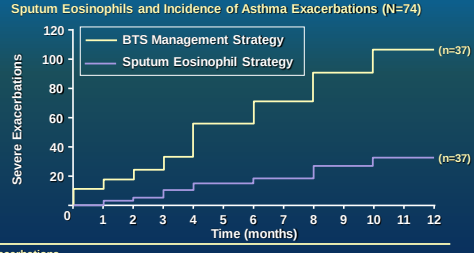
*Reference strategy based on symptoms, β_2-agonist use, peak expiratory flow (PEF) variability, and FEV_1.
†AHR based on symptoms, β_2-agonist use, PEF variability, FEV_1, and AHR to methacholine challenge.
Adapted from Sont JK et al. *Am J Respir Crit Care Med*. 1999;159:1043-1051.

Summary of Sont et al study results:

- Patients treated by AHR strategy had a 1.8 fold lower rate of mild exacerbations vs patients using the reference strategy (using existing guidelines with respect to measuring symptoms and lung function).
- FEV1 improved to a greater extent in the AHR strategy.
- In the AHR strategy the average difference in ICS dose over the 2-year period had a median difference of 400 µg/day more in the AHR group
- There was a greater reduction of the subepithelial reticular layer in the AHR group.

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

Monitoring Asthma Inflammation: Sputum Eosinophils



Number of Exacerbations									
BTS Management Strategy	0	12	19	26	35	59	75	93	109
Sputum Eosinophil Strategy	0	1	4	7	12	17	21	30	35

BTS = British Thoracic Society.
Adapted from Green RH et al. *Lancet*. 2002;360:1715-1721.

Summary of Green study results:

- Patients in the sputum management group had significantly fewer severe asthma exacerbations than patients in the BTS group (35 vs 109; *P*=.01)
- In the sputum management study, there was no difference in mean ICS dose between groups overall.
- However, a subgroup analysis of patients with noneosinophilic inflammation revealed a mean difference of 1425 µg/day, with decreased ICS use in the sputum strategy group
- Therefore monitoring sputum eosinophils could help identify asthma patients with eosinophilic inflammation who are responsive to CS.

Green RH et al. *Lancet*. 2002;360:1715-1721

Limitations of Sputum Eosinophils as a marker for asthma severity

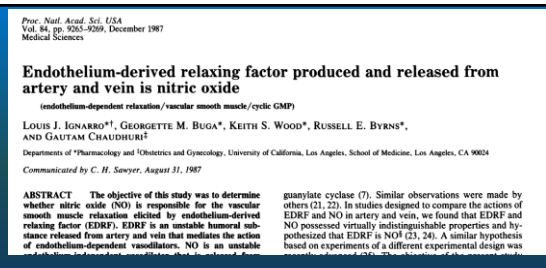
- Even though there is a relationship between number of eosinophils and asthma severity, there is much scatter.
- In the European Network for Understanding Mechanism of Severe Asthma (ENFUMOSA), eosinophils did not distinguish severe asthmatics from those well controlled on low or moderate doses of ICS.

Louis R et al. A J Respir Crit Care Med 2000;161:9-16.
ENFUMOSA. Eur Respir j. 2003;22:470-477.

Monitoring Asthma Inflammation: FE_{NO}

- A biomarker that has been increasingly used in clinical practice, now has CPT billing code: 95012.
- 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
- May be useful to identify eosinophilic asthma phenotype.

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



Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 9265–9269, December 1987
Medical Sciences

Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide

(endothelium-dependent relaxation/vascular smooth muscle/cyclic GMP)

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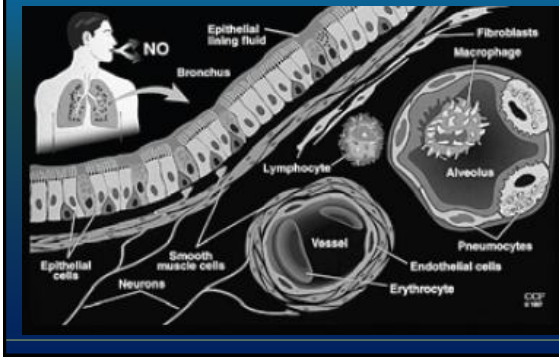
Communicated by C. H. Sawyer, August 31, 1987

ABSTRACT The objective of this study was to determine whether nitric oxide (NO) is responsible for the vascular smooth muscle relaxation elicited by endothelium-derived relaxing factor (EDRF). EDRF is an unstable humoral substance released from artery and vein that mediates the action of endothelium-dependent vasodilators. NO is an unstable

guanylate cyclase (7). Similar observations were made by others (21, 22). In studies designed to compare the actions of EDRF and NO in artery and vein, we found that EDRF and NO possessed virtually indistinguishable properties and hypothesized that EDRF is NO‡ (23, 24). A similar hypothesis based on experiments of a different experimental design was

- Noble Prize in Physiology or Medicine in 1998 awarded to Furchgott, Ignarro, & Murad for "discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system."

Sources for nitric oxide detected in exhaled air



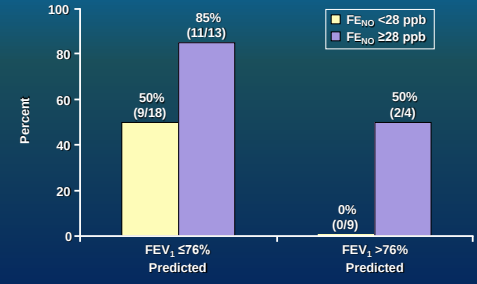
FE_{NO}: Diagnostic Properties

	Asthma (n = 17)		Nonasthma (n = 30)		Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
	Yes	No	Yes	No				
Bronchodilator reversibility >12%	7	10	0	30	—	—	—	—
Bronchial hyperresponsiveness <20 mL	15	2	0	30	—	—	—	—
Peak flow variation >20%	0	17	0	29*	0	100	NA	70
Peak flow improvement with steroid >15%	4	13	0	29*	24	100	100	69
FEV_1 <80% predicted	5	12	0	30	29	100	100	71
FEV_1 <90% predicted	6	11	2	28	35	93	75	72
FEV_1/FVC ratio <70%	6	11	0	30	35	100	100	73
FEV_1/FVC ratio <80%	8	9	6	24	47	80	57	73
FEV_1 improvement with steroid >15%	2	15	0	29*	12	100	100	66
Sputum eosinophils >3%	12	2*	3	23*	86	88	80	92
FE_{NO} >20 ppb	14	2†	6	22†	88	79	70	92

- Asthma diagnosed by bronchodilator reversibility and/or bronchial hyperresponsiveness (shown above purple line)
- Comparison of FE_{NO} with other diagnostic tests is shown at bottom

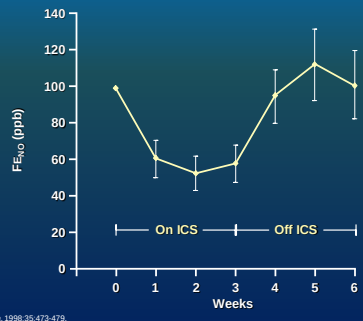
FVC = forced vital capacity; ppb = parts per billion.
*Patient unable or unwilling to complete procedure.
†Technical difficulties prevented completion of FE_{NO} measurements at 50 mL/second.
Smith AD et al. *Amer J Respir Crit Care Med*. 2004;169:473-478.

FE_{NO} and FEV_1 Predict Risk of Exacerbations



Adapted from Gelb AF et al. *Chest*. 2006;129:1492-1499.

FE_{NO}: Possible Detection of Noncompliance With ICS



Silkoff P et al. *J Asthma*. 1998;35:473-479.

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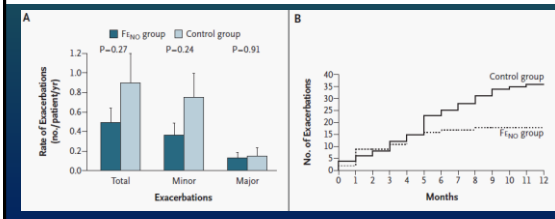
Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma

Andrew D. Smith, M.B., Ch.B., Jan O. Cowan, Karen P. Brassett, G. Peter Herbison, M.Sc., and D. Robin Taylor, M.D.



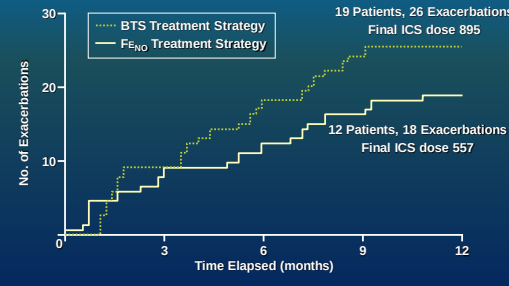
Smith AD et al. *N Engl J Med*. 2005;352:2163-2173.

Summary of Smith et al study results:

- This study enrolled 110 patients with chronic asthma on regular ICS therapy for 6 months. At the end of run-in, patients began receiving fluticasone 750 µg/day.
  - In phase 1, the dose was adjusted at each visit according to nitric oxide level (FE_{NO} group) or asthma control (control group).
  - In phase 2, a patient's ICS dose could be increased according to the same protocol, but it could not be decreased
- At the end of 12 months, patients in the FE_{NO} group had used significantly less ICS (mean=370 mcg) than those in the control group (mean=641 mcg) (*P*=.003).
- There was a non-significant reduction (45.6%) in exacerbation rates in the FE_{NO} group.

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

Other Studies Suggest That Use of a FE_{NO} Treatment Strategy Does Not Improve Outcomes



P=.43.
Adapted from Shaw DE et al. *Am J Respir Crit Care Med*. 2007;176:231-237.

Summary of Shaw et al study results:

- 118 patients with asthma were randomized to a single-blind trial of ICS therapy based on FE_{NO} measurements (n=58) or British Thoracic Society guidelines (n=60).
- In the FE_{NO} group, the mean rate of exacerbations was 0.33 per patient per year (18 exacerbations among 12 subjects), compared with 0.42 in the control group (26 exacerbations among 19 subjects; *P*=.43)
- The FE_{NO} group used 11% more inhaled corticosteroid overall compared with the control group (not significant). However, the final daily dose of ICS was significantly lower in the FE_{NO} group compared with control (557 versus 895 µg; *P*=.028)

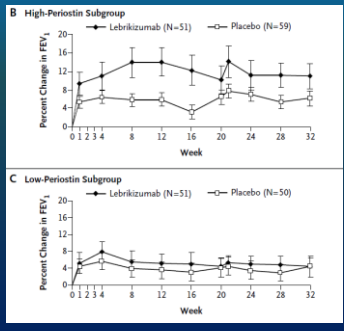
Shaw DE et al. *Am J Respir Crit Care Med*. 2007;176:231-237

Other potential biomarkers-Periostin

- Periostin is a systemic biomarker of airway eosinophilia in asthma.
- Elevated periostin was found to correlate with three-gene bronchial epithelial Th2 signature in a subset of asthmatics.
- Elevated periostin levels associated with eosinophilic airway inflammation.

Arron JR, Jia GQ, et al Am J Respir Crit Care Med 2011;183:A4455.

Anti-Interleukin-13 impact on Asthma



- In High-Periostin group, FeNO fell from baseline mean = 37 by 34.4%.
- In Low-Periostin group, FeNO fell from baseline mean = 25.3 by 4.3%.

Corren et al, N Engl J Med 2011;365:1088-1098.

Summary: Biomarkers have potential utility in the assessment of airway inflammation in patients with asthma and potential in helping to monitor control.

- AHR is time- and labor-intensive
  - Methacholine may be more useful for diagnosis
  - Mannitol has potential for assessing responsiveness to therapy
- Sputum eosinophils
  - Excellent research tool
  - Clinically useful in predicting exacerbations and ICS dose titration
- FeNO
  - Greatest ease of use
  - Useful for ruling out a diagnosis of asthma, and possibly for assessing ICS adherence
- Future biomarkers
  - Periostin
  - ?

New Paradigm for "Asthma Control"

Conclusions

- NAEPP guidelines recognize control as the goal of asthma management.
- At this time Expiratory Spirometry is an effective tool to monitor asthma control.
- Biomarkers use may be helpful in the future to help monitor control for asthma patients.