

Acute Physiologic Characteristics and Long Term Clinical Consequences of Asthma Exacerbations

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Stephen P. Peters, MD, PhD Disclosure

- **Basic and Clinical Research**
 - NHLBI (AsthmaNet, SARP, SPIROMICS)
 - ALA (ACRC)
- **Book Chapters**
 - UpToDate
- **Pharmaceutical Trials**
 - Actelion, Amgen, AstraZeneca, Boehringer-Ingelheim, Centocor, Cephalon, Genentech, GlaxoSmithKline, Forest, Medimmune, Sanofi
- **Advisory Boards**
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- **Speakers' Bureaus**
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- **Editorial Boards**
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 - Resp Research, Assoc Ed
 - J Allergy
 - Case Reports in Medicine
 - US Resp Disease
 - J Pulm Resp Medicine
 - Clin Exp Med Sciences
 - JACI: *In Practice*

Goals and Learning Objectives

- **Discuss Acute Asthma Exacerbations with Respect to**
 - Risk Factors and Associations for Exacerbations
 - Frequent Exacerbator Phenotype
 - Kinetics and Physiology of Manifestations
 - Impact on Patients and Long Term Consequences

**Frequent Exacerbator ($\geq 3/\text{yr}$)
Phenotype in SARP** Denlinger, SARP, et al., AJRCCM (In press)

**Unpublished SARP
Data to be
Presented Here**

**Frequent Exacerbator Phenotype ($\geq 2/\text{yr}$)
in BIOAIR** Kupczyk, et al., Clin Exp Allergy 2013; 44:212-221

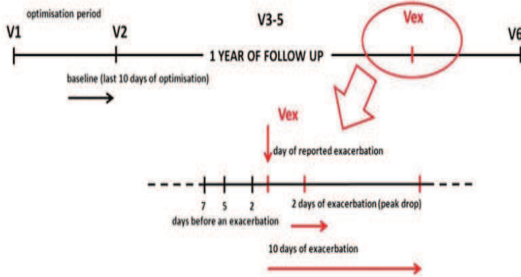
Variable	OR (95% CI)
FeNO > 45 ppb	4.32 (1.02, 18.31)
Smoking	2.90 (1.15, 7.35)

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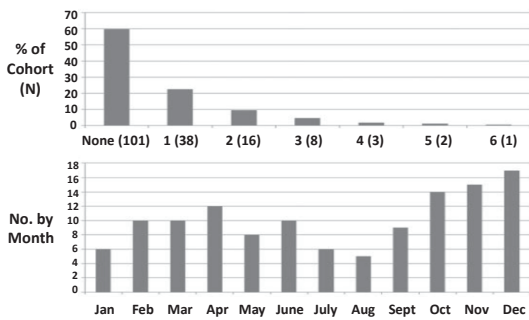
BIOAIR – Physiology of Exacerbations - 1

Kupczyk, et al., Thorax 2013; 68:611–618



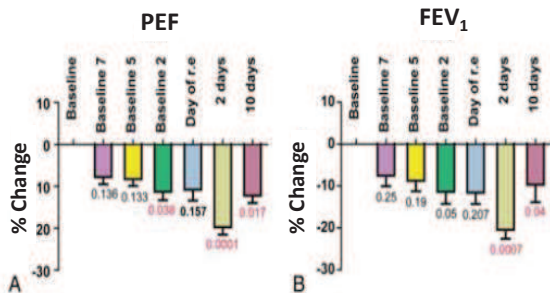
BIOAIR – Frequency of Exacerbations

Kupczyk, et al., Thorax 2013; 68:611–618



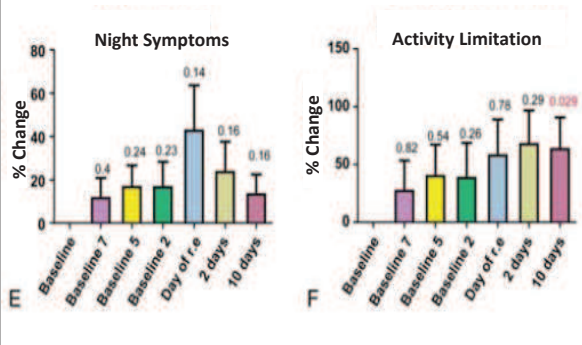
BIOAIR – Physiology of Exacerbations - 2

Kupczyk, et al., Thorax 2013; 68:611–618



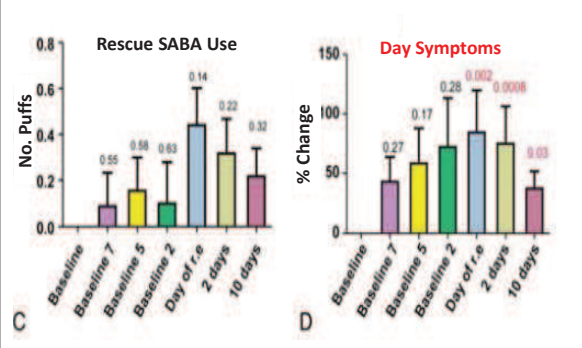
BIOAIR – Physiology of Exacerbations - 3

Kupczyk, et al., Thorax 2013; 68:611–618



BIOAIR – Physiology of Exacerbations - 4

Kupczyk, et al., Thorax 2013; 68:611–618

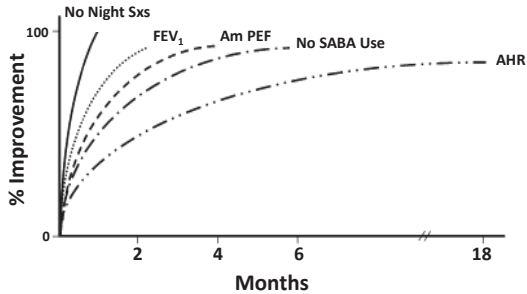


Symptoms: Portend Impending Exacerbation and Drive Treatment

- BIOAIR – increased symptoms preceded lung function changes and increased rescue β -agonist use (Thorax 2013; 68:611–618)
- Chan-Yeung – symptoms started to increase 2 days before the first day of exacerbation and that this occurred before the PEF fell (AJRCCM 1996;154:889-893)
- Dennis – “of all the diary card variables an increase in daytime symptoms is strongly predictive of additional oral or increased inhaled corticosteroid usage” (Clin Exp All 2005; 35:308-312)
- FACET - 73% of FACET exacerbations resulted in treatment with oral corticosteroids in response to increasing symptoms rather than a fall in morning PEF (AJRCCM 1999; 160:594–599)

Kinetics of Improvement after ICS

Reddell, et al., AJRCCM 2009; 180:59-99



BIOAIR – Detecting Exacerbations

Kupczyk, et al., Thorax 2013; 68:611–618

Table 3 Sensitivity and specificity of combined parameters to detect severe exacerbations

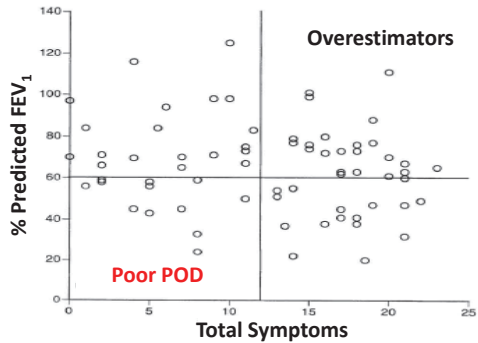
Definition of exacerbation	Severe exacerbations in the whole asthma cohort	
	Sensitivity (%)	Specificity (%)
20% decrease in PEF on 2 consecutive days and 20% increase in day symptoms on 2 consecutive days	13.3	99.5
20% decrease in PEF on 2 consecutive days or 20% increase in day symptoms on 2 consecutive days	65.0	94.9
20% decrease in FEV ₁ on 2 consecutive days and 20% increase in day symptoms on 2 consecutive days	13.2	99.3
20% decrease in FEV ₁ on 2 consecutive days or 20% increase in day symptoms on 2 consecutive days	60.4	94.8

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Perception of Airway Obstruction

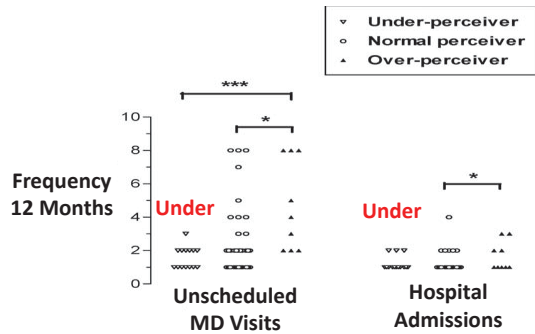
Teeter and Bleecker, CHEST 1998; 113:272-77



Insert "Perception of Dyspnea"
Question Here

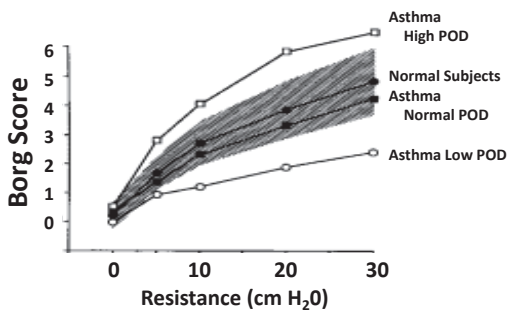
Perceptions of Dyspnea – 1

Loh and Teh, J Asthma 2009; 46:529-534



Perceptions of Dyspnea – 2

Magadle, et al., CHEST 2002; 121:329–333



Perceptions of Dyspnea – 2

Magadle, et al., CHEST 2002; 121:329–333

ED Visits, Hospitalizations, Near Fatal Asthma, Deaths in 113 Patients with Asthma

	Low POD n = 29	Normal POD n = 67	High POD n = 17
ED Visits	32	8	14
Hospitalizations	22	4	3
Near-Fatal Asthma	13	2	1
Deaths	6	1	0

Data are Number of Events; Patients may have had more than one episode.

Recurrent Exacerbations and Enhance Airway Closure

Johannes, et al., AJRCCM 2000; 161:1902–1906

Parameter (% pred)	Difficult-to-control Asthma		p Value
	Stable Asthma		
FEV ₁	89.0 ± 4.6	92.9 ± 4.3	0.54
TLC	106.7 ± 4.0	101.7 ± 4.3	0.40
FRC	98.6 ± 6.6	98.7 ± 4.5	0.99
RV	113.1 ± 7.8	100.9 ± 7.1	0.26
RV/TLC	103.5 ± 4.7	95.8 ± 3.8	0.21
dN ₂	142.7 ± 16.3	116.0 ± 20.2	0.23
CV/VC	159.5 ± 26.8	98.8 ± 12.5	0.024
CC/TLC	114.0 ± 6.4	99.9 ± 3.6	0.030

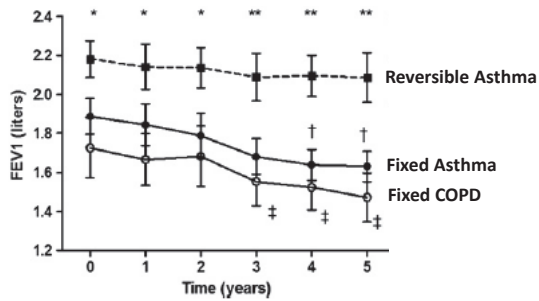
Definition of abbreviations: CC/TLC = ratio of closing capacity to total lung capacity; CV/VC = ratio of closing volume to vital capacity; RV/TLC = ratio of residual volume to total lung capacity; dN₂ = slope of Phase 2 of the nitrogen expiration curve.

All values (% predicted) are expressed as mean ± SEM. RV/TLC = RV as ratio of TLC; dN₂ = slope of phase 3; CV/VC = closing volume as ratio of vital capacity; CC/TLC = closing capacity as ratio of TLC.

Insert “Lung Function Decline and Exacerbations: Cause and Effect?”
Question Here

Fixed Airflow Obstruction* and Lung Function Decline Over 5 Years

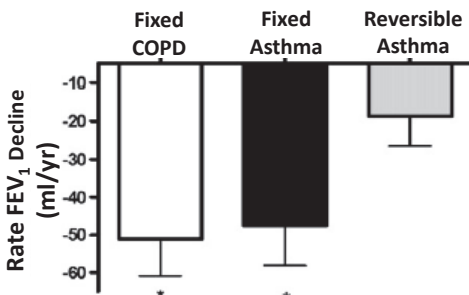
Cantoli, et al., J Allergy Clin Immunol 2010; 125:830-837



*FEV1/FVC < 70% after albuterol and prednisolone

Fixed Airflow Obstruction* and Lung Function Decline Over 5 Years

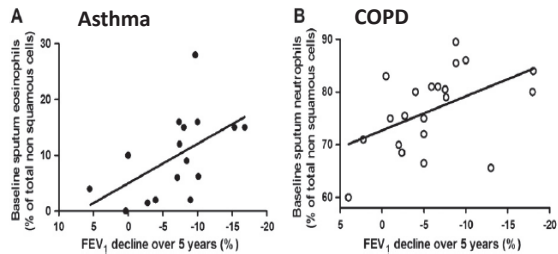
Cantoli, et al., J Allergy Clin Immunol 2010; 125:830-837



*FEV1/FVC < 70% after albuterol and prednisolone

Fixed Airflow Obstruction* and Lung Function Decline - Inflammation

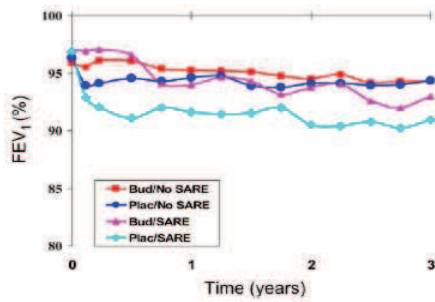
Cantoli, et al., J Allergy Clin Immunol 2010; 125:830-837



*FEV₁/FVC < 70% after albuterol and prednisolone

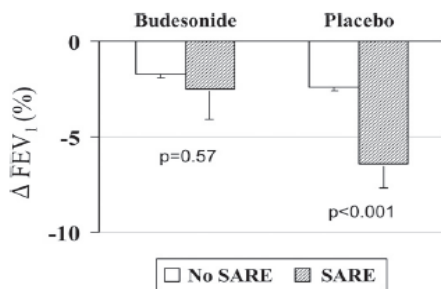
Severe Asthma Exacerbations and Lung Function Decline (3 yrs, post-BD) - START

O'Byrne, et al., AJCCM 2009; 179:19-24



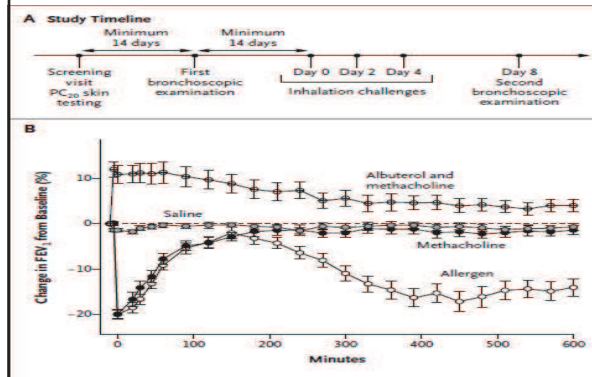
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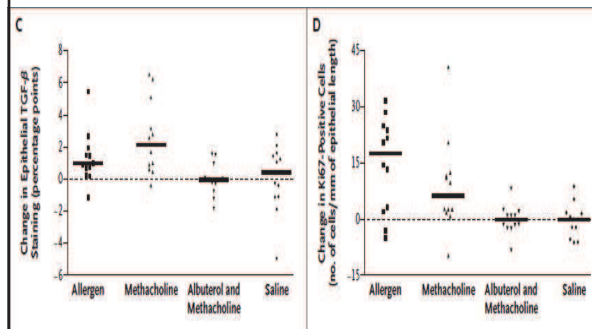
Bronchoconstriction and Airway Remodeling

Grainge, et al., NEJM 2011; 364:2006-2015



Bronchoconstriction and Airway Remodeling

Grainge, et al., NEJM 2011; 364:2006-2015



Summary and Conclusions

- Risk Factors for Exacerbations include **Recent Prior Exacerbations, More Severe Asthma, High BMI, Poor Symptom Control and Excess β -Agonists Use, and Airflow Limitation**
- Exacerbations are a **Major Cause of the Morbidity** Associated with Asthma
- **Airflow Limitation and Decrease in Lung Function** Appear to be Both Risk Factors for Exacerbations and a **Result of Them**
