December 9, 2012
Particle Deposition and Small Airways In Asthma

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Small Airways Working Group

The WAO's Small Airways Diseases aims to provide a credible, evidence-based, global platform for physicians and other health care professionals around the world to have ease-of-access to the most relevant scientific, clinical and educational resources on small airway disease.

This program is made possible through an unrestricted educational grant from:

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Meet the Web Editor of the Small Airways Working Group

Ves Dimov, MD
Allergist/Immunogist
Assistant Professor of Pediatrics and Medicine
University of Chicago, Illinois
Editor-at-Large, WAO Web Editorial Board

Dr. Ves Dimov, the working group's Web Content Editor, oversees the site's scientific literature database, ensuring it is current and relevant. Each month he writes a column, "What Is New in Small Airways Research" in which he highlights new research articles of particular value to physicians who treat patients with small airways diseases.

"Try this—I just bought a hundred shares."

Disclosure Statement
Lanny J. Rosenwasser, MD

- RESEARCH STUDIES
  Genentech, Novartis, National Institutes of Health
- CONSULTANT
  A-Z, Genentech, Novartis, Regeneron, Sanofi-Aventis
- SPEAKERS' BUREAU
  Alcon, A-Z, Genentech, Novartis

Learning Objectives

- Understand the Concept of Particle Deposition
- Understand How Particle Size Impacts Deposition of Inhaled Asthma Medications
- Understand the Relationship of Particle Size and Deposition to Physiologic Responses of Small Airways

Characterization of aerosol output from various nebulizer/compressor combinations

Colin Reisner, MD; Rohit K. Katial, MD; B. Bucher Bartelson, PhD; Andrea Buchmeir, CCRC; Lanny J. Rosenwasser, MD; and Harold S. Nelson, MD

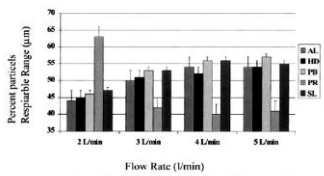
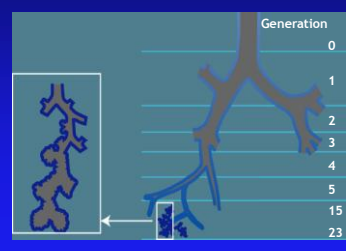


Figure 4. Mean percentage of particles in respirable range by nebulizer and flow rate. Percentage of particles in the respirable range (1 to 5 µm) was measured during continuous nebulization to the point where the nebulizer output fell 8-fold. AL = Airlife Misty Nebulizer; HD = Hudson Micromist; PB = Puritan Bennett Raindrop; PR = Pari LC Jet; and SL = Salter 8900.

Ann Allergy Asthma Immunol.
2001 May;86(5):566-74.

The Disease Process in Asthma is Located in All Parts of the Bronchial Tree, Small Airways and Alveoli.



Workgroep Inhalatie Technologie, Jun 1999.

Small Airway Inflammation in Asthma: Background

- Inflammation and airway remodeling in asthma extends into the small airways (< 2 mm diameter).
- This small airway inflammation may contribute to difficult-to-control asthma.

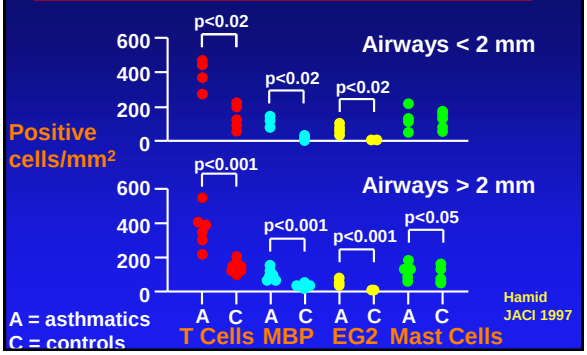
Inflammation of Small Airways in Asthma

Q Hamid et al. J Allergy Clin Immunol 1997;100:44-51

Surgical lung specimens from 6 patients with asthma and 10 controls were examined.

There was a similar inflammatory process present in the peripheral (< 2mm diameter) compared with the central airways.

Immunohistochemical Markers in the Large & Small Airways



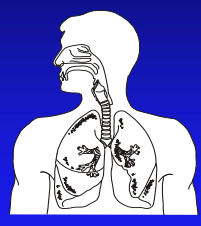
Difficult-to-Control Vs. Stable Asthmatics

- There were no significant differences in lung function except increased closing volume and closing capacity in the difficult to treat asthmatics.
- "This is indicative of small airway pathology in these patients"
- "Delivery of anti-inflammatory medication to the small airways in this subgroup is of specific clinical relevance".

AJRCCM 2000;161:1902-6

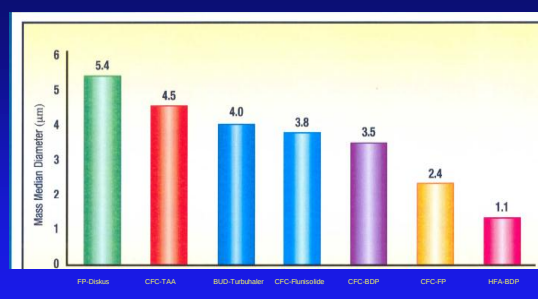
Andersen Sampler Simulates Human Respiratory System

STAGE 0	11+	Oropharynx
STAGE 1	7.0-11.0	Oropharynx
STAGE 2	4.7-7.0	Oropharynx
STAGE 3	3.3-4.7	Trachea and primary bronchi
STAGE 4	2.1-3.3	Secondary bronchi
STAGE 5	1.1-2.1	Terminal bronchi
STAGE 6	0.65-1.1	Respiratory bronchioles
STAGE 7	0.43-0.65	Alveoli



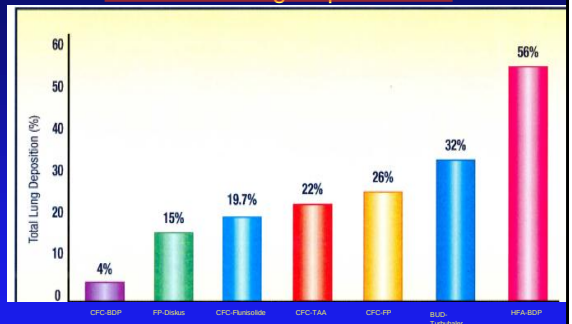
Newsom SWB. Airborne Particles from Latex Gloves in the Hospital Environment. Eur J Surg 1997; Suppl 579: 31-33.

Steroid Particle Size



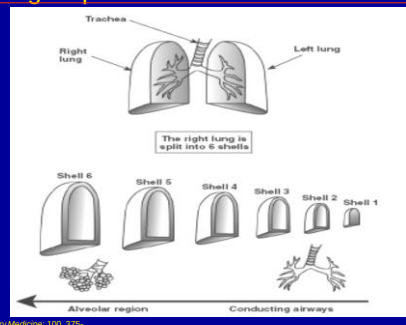
Martin R. J. *Allergy Clin Immunol* 2002;109:S447-60.
Adapted from Bensch and Newman. *AJRCCM* 2001;163(5) A440 at ERS 200

Steroid Lung Deposition



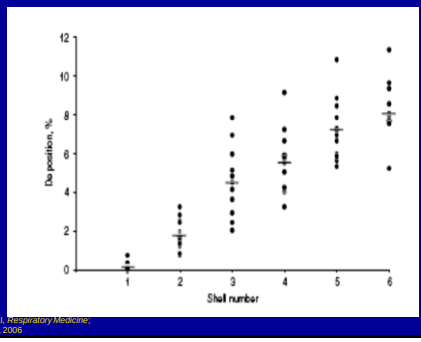
Martin R. *J Allergy Clin Imunol* 2002:109:S447-60. Adapted from Bensch and Newman. AJRCCM 2001; 163 (3) A440 AT ERS 2000

Lung Deposition of HFA-ciclesonide



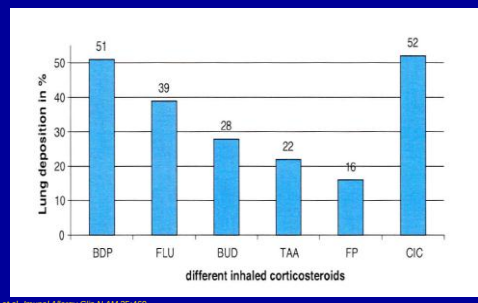
Newman et al, *Respiratory Medicine*: 100, 375-385, 2006

Lung Deposition of HFA-ciclesonide



Newman et al, *Respiratory Medicine*: 100:375-384, 2006

Lung Deposition of HFA Inhaled Corticosteroids



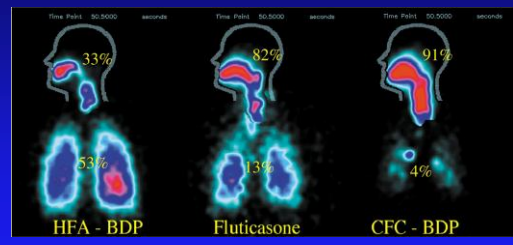
Hubner et al, *Imunol Allergy Clin N AM* 25:469-488, 2005

Study Design

- Crossover design
- 9 healthy subjects aged 18-52 years
- Randomized to receive inhaled technetium-99m labeled
  - HFA-beclomethasone
  - CFC-fluticasone
  - CFC-beclomethasone

Leach CL et al. *Am J. Respir Crit Care Med.* 2000;161(3): A34.

Comparison of lung deposition in the same subject



Leach CL *et al. Am J Respir Crit Care Med* 2000; 16 (3): A34

Conclusions

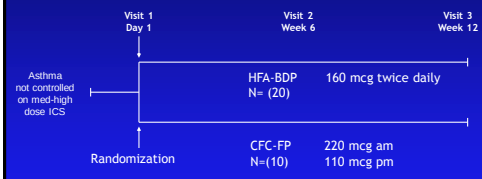
- HFA-BDP is evenly distributed throughout the lungs and therefore reaches all sites of inflammation
- CFC-fluticasone is deposited primarily in the large and intermediate airways
- CFC-BDP is deposited almost exclusively in the large airways

Hydrofluoroalkane-134a Beclomethasone or Chlorofluorocarbon Fluticasone: Effect on Small Airways in Poorly Controlled Asthma

Torpong Thongngarm, MD, Philip E Silkoff, MD, Willaim S Kossack MS, Harold S. Nelson, MD. J Asthma 2005;42:257-63

Study Design

Randomized, Open Label, Parallel Group



Thongngarm et al. *J Asthma* 2005;42:257-63

Study Design

Endpoints

	Screening Period	Visit 1	Visit 2	Visit 3
Pre-Bronchodilator				
Spirometry	X	X	X	X
Closing volume	X			X
Post-Bronchodilator (albuterol x 2 Puffs)				
Spirometry	X			X
Plethysmography	X			X

Thongngarm et al. *J Asthma* 2005;42:257-63

Results: Patient Demographics

	HFA-BDP (20)	CFC-FP (9)	
FEV_1	59%	55%	
FEV_{25-75}	33%	28%	
RV	196%	205%	
CV (L)	0.51	0.57	
CV/VC	18	16	
ICS (med/high)	5/15	3/6	
Albuterol P/D	4	0.4	$p < 0.05$
Asthma score	4	1.3	$p = .11$

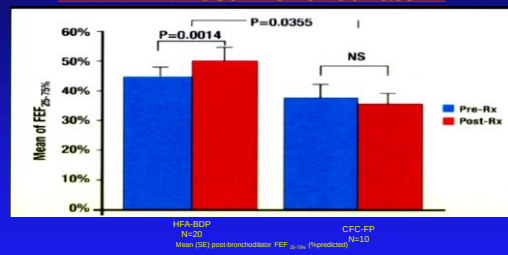
Exacerbations

- During the blinded period 5/20 subjects receiving HFA-BDP and 0/10 receiving CFC-FP experienced exacerbations treated with prednisone.
- Subjects were tested at least one month following their last prednison.
- Post-treatment parameters in these 5 subjects fell within +/- one SD of those of the other 15 HFA-BDP subjects.

Results: Pulmonary Function

Parameter	HFA-BDP			CFC-FP		
	Pre	Post	p	Pre	Post	p (BvF)
CV (L)	.51	.44		.57	.76	<.005
CV/VC	18	14.2	(.02)	15.8	18.8	<.02
RV%	196	184	(.05)	205	205	
FEV_1 Post Br Dil	67.6	71.9	(02)	66.4	67	
FEF_{25-75} (post)	42.5	51	(.002)	36.6	36	<.04

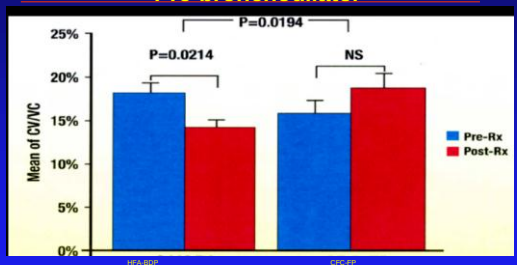
Clinical Results
FEF 25%-75% Post Bronchodilator



•Patients on HFA-BDP showed significant improvement in FEF25-75% pre-bronchodilator (P=0.0016) and post bronchodilator (P=0.0014).
•There was no significant change in FEF25-75% pre-bronchodilator and post-bronchodilator in the CFC-fluticasone (CFC-FP) group.

Thongngarm et al. J Asthma 2005;42:257-63

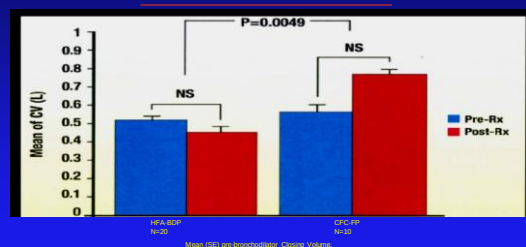
Small Airway Patency
Closing Volume/Vital Capacity (CV/VC)
Pre-bronchodilator



•Patients on HFA-BDP showed a significant decrease of 3.74% I n pre-bronchodilator closing volume/vital capacity (CV/VC ratio (P=0.0214).
•The CFC-fluticasone (CFC-FP) group recrobed a mean increase of 3.0% (P=0.34).

Thongngarm et al. J Asthma 2005;42:257-63

Small Airway Patency
Closing Volume/Vital Capacity (CV/L)
Pre-bronchodilator



•Patients on HFA-BD trended toward a mean decrease in closing volume.
•Patients on CFC-Fluticasone trended towards an increase in closing volume.

Thongngarm et al. J Asthma 2005;42:257-63

Results: Diary & Peak Flows

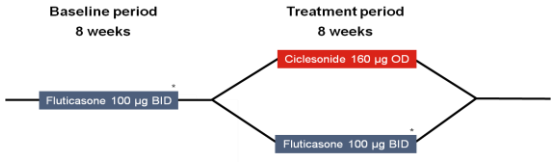
Parameter	HFA-BDP		p(B)	CFC-FP		p(BvF)
	pre	post		pre	post	
AM-PEF	303	333	(.04)	300	301	NS
Phlegm	2	.14	(.05)	0	1	<.03
Albuterol use	4	.28	(.02)	.4	0	<.05

Conclusions

In patients with moderate to severe persistent asthma who were not adequately controlled on medium to high doses of inhaled corticosteroids.

The addition of HFA-BDP provided greater effects than the addition of a similar dose of CFC-FP on small airway parameters

Comparison of ciclesonide and fluticasone proprionate on small airway function



Randomized, open-label, parallel group study with a treatment period of 8 weeks to compare effectiveness of small particle ICS (ciclesonide) and large particle ICS (fluticasone DPI) on small airway function

Fluticasone propionate *DPI: particle size 5.4 µm diameter
Ciclesonide HFA: particle size of 1.1 µm diameter

Hoshino M. *Allergology International* **2010**;59:59-66

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Impulse oscillometry (IOS), a measure of small and large airway function

- R5: large and small airway resistance (5 Hz)
- R20: large airway resistance (20 Hz)
- R5-R20: small airway resistance
- X5: capacitive reactance in small airways (5 Hz)
- AX: area of low-frequency reactance

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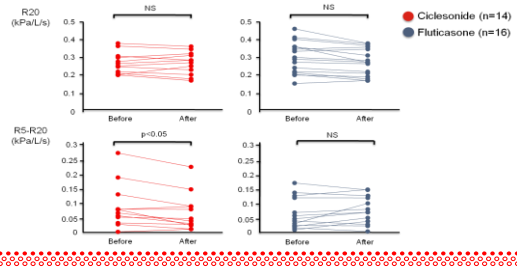
Changes in large and small airway resistance with ciclesonide and fluticasone



Data are presented as mean values

Hoshino M. *Allergology International* **2010**;59:59-66

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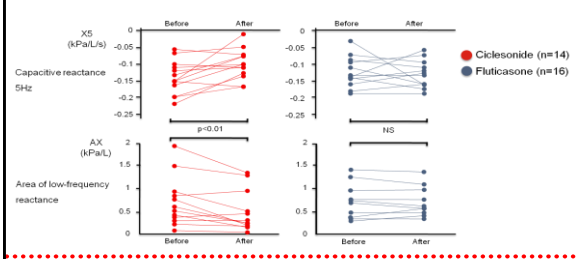
Changes in capacitive reactance in small airways and in area of low-frequency reactance



Data are presented as mean values

Hoshino M. *Allergology International* **2010**;59:59-66

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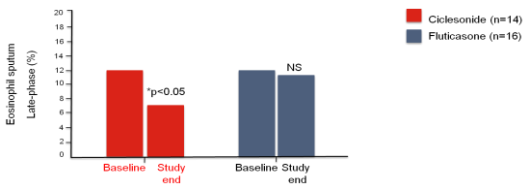
Changes in eosinophil percentage of late-phase sputum with ciclesonide and fluticasone propionate



- Significant reduction of eosinophils in late-phase sputum in the ciclesonide group
- The percentage of early-phase sputum eosinophils remained unchanged in both groups

Data are presented as mean values
* versus baseline

Hoshino M. *Allergology International* **2010**;59:59-66

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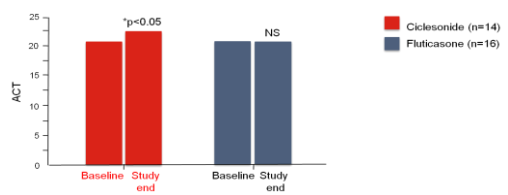
Changes in asthma control test (ACT) scores in the ciclesonide and fluticasone propionate groups



- Ciclesonide improved asthma control significantly
- Lung function was maintained in both groups

Data are presented as mean ± SD
* versus baseline

Hoshino M. *Allergology International* **2010**;59:59-66

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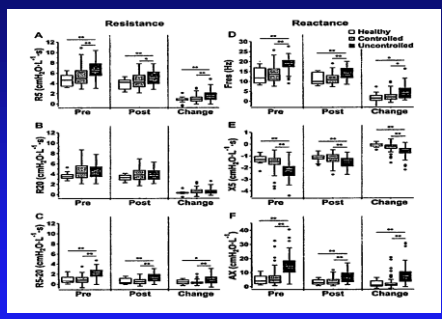
Summary and conclusions

- Ciclesonide improves small airway function and inflammation
- In mild patients pre-treated with fluticasone DPI, asthma control improved significantly if switched to the small particle ICS ciclesonide
- This study provides evidence that IOS and late-phase induced sputum allows detection of changes in the small airways that can not be detected by spirometry

Small Airways and Pediatric Asthma

JACI, 129, 671-678; 2012

Yixin Shi, MS,[a] Anna S. Aledia, BS,[a,c] Ahramahzd V. Tatavoosian,BS,[a] Shruthi Vijayalakshmi,[a] Stanley P. Galant, MD,[e,f] and Steven C. George, MD, PhD[a,b,c,d] *Irvine and Orange, Calif*



The Utility of Forced Expiratory Flow between 25% and 75% of Vital Capacity in Predicting Childhood Asthma Morbidity and Severity

Journal of Asthma, 49(6): 586–592, 2012

DEVIKA R. RAO, M.D.,[1,*] JONATHAN M. GAFFIN, M.D., M.M.SC.,[1] SACHIN N. BAXI, M.D.,[2] WILLIAM J. SHEEHAN, M.D.,2 ELAINE B. HOFFMAN, PH.D.,[3] AND WANDA PHIPATANAKUL, M.D., M.S.[2]

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[2]Department of Allergy and Immunology, Boston Children's Hospital, Boston, MA, USA.

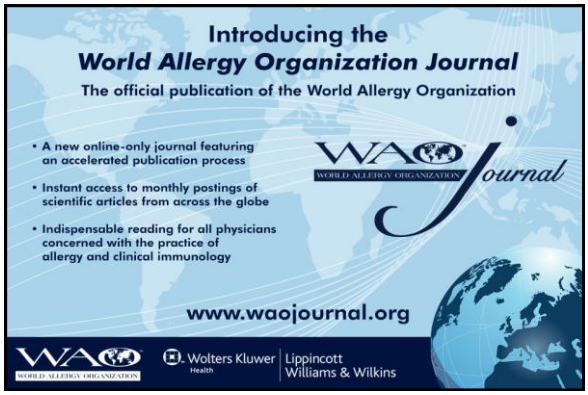
[3]Harvard School of Public Health, Harvard Medical School, Boston, MA, USA.

	All subjects (n = 744)	Normal spirometry[a] (n = 35)	Low FEV_1/FVC[b] (n = 36)	Low FEF_{25-75}[c] (n = 37)
Age at testing (years)				
10–12	39% (288)	34% (2)	36% (13)	38% (14)
13–15	38% (285)	20% (7)	25% (9)	14% (5)
16–18	23% (173)	46% (16)	39% (14)	48% (18)
Gender				
Male	54% (399)	49% (17)	50% (18)	49% (18)
Race				
White	86% (637)	66% (23)	64% (23)	62% (23)
Black	10% (74)	23% (8)	22% (8)	22% (8)
Latino	3% (25)	11% (4)	14% (5)	16% (6)
Asian	1% (6)	0% (0)	0% (0)	0% (0)

TABLE 4.—Severity and morbidity of subjects with normal FEV_1, low FEV_1/FVC, and low FEF_{25-75} in age, race, gender-matched controls.

	Normal spirometry[a] (n = 35)	Low FEV_1/FVC[b] (n = 36)	Low FEF_{25-75}[c] (n = 37)
Severity of asthma			
Mild	72% (26)	39% (14)	19% (7)
Moderate persistent	19% (7)	47% (17)	54% (20)
Severe persistent	8% (21)	14% (5)	27% (10)
Clinical history			
Hospitalizations	20% (7)	19% (7)	30% (11)
ICU admissions	3% (1)	8% (21)	8% (21)
Steroids	28% (10)	50% (18)	60% (22)
ED visits	25% (9)	33% (12)	46% (17)
Exacerbations	25% (9)	60% (22)	70% (26)
Use of controller	69% (25)	100% (36)	95% (35)

Notes: Groups are age, race, gender-matched. FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; ED, emergency department.
[a]Normal FEV_1, FEV_1/FVC, and FEF_{25-75}.
[b]Normal FEV_1, low FEV_1/FVC, and normal FEF_{25-75}.
[c]Normal FEV_1, low FEV_1/FVC, and low FEF_{25-75}.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