AAAAI The Life Spectrum of Asthma 2016

Reducing/Eliminating Asthma Exacerbations: Immunopathologic Features of Asthma Exacerbations

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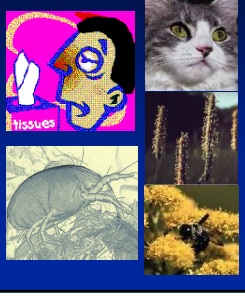
Causes of Asthma Exacerbations

- Poor underlying control
- Environmental factors
  - VRIs
  - Allergen exposure
  - Air pollution
  - Bacterial infections
  - Stress
  - Exercise/cold air
  - Occupational exposure



Asthma Exacerbations

- Viruses cause asthma exacerbations in adults and children
- RVs cause ~60% of virus-induced exacerbations of asthma
- The response to viral infection is shaped by the host's antiviral response
- Worsening of airway inflammation during exacerbations may be related to accelerated loss of lung function and structural changes

Viruses Detected During Asthma Exacerbations in Children

	Method of detection				
Virus	PCR	Culture	Immuno-fluorescence	Antibody rise by ELISA	Total
Picornaviruses	146	47			147*
Coronavirus	17	14		21	38
Influenza viruses		14	10	20	21
Parainfluenza viruses 1, 2, and 3		6	6	18	21
RSV		6	6	12	12
Other		2	1	2	3

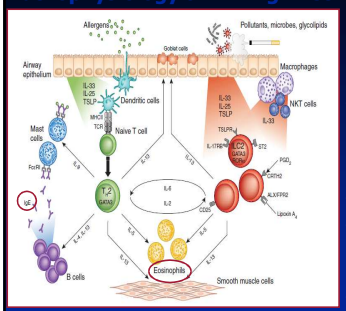
*108 school age children; viruses detected 80% of exacerbations; 84 of 147 picornaviruses identified as RV on further testing.
ELISA=enzyme-linked immunosorbent assay.
Reprinted from *BMJ*. 1995;310:1225-1229, with permission from the BMJ Publishing Group.

Viruses Detected in Symptomatic Asthma Exacerbations in Adults

Pathogen	Number	Percent of all episodes
RV	76	33.2
HCV OC43	21	9.2
HCV 229E	15	6.6
Influenza B	2	0.9
Parainfluenza	5	2.2
RSV	2	0.9
Chlamydia psittaci	3	1.3
Dual infection	5	2.2

138 adults with 280 exacerbations
RV=rhinovirus; HCV=human coronavirus; RSV=respiratory syncytial virus.
Nicholson KG et al. *BMJ*. 1993;307:982.

Pathophysiology of T2-High Asthma



High eosinophil levels cause[1–4]:

- Recruitment and activation of immune and structural cells
- Airway inflammation
- Airway wall fibrosis, thickening, and remodeling
- Inadequately controlled asthma symptoms and increased

ALX/FPR2 = receptor for lipoxin A4; CRTH2 = chemoattractant receptor-homologous molecule Th2; FcεRI = high-affinity receptor for IgE; GATA3 = GATA-binding protein 3; Ig = immunoglobulin; IL = interleukin; NKT = natural killer T; PGD_2 = prostaglandin D_2; RORα = retinoic acid receptor–related orphan receptor α; TSLP = thymic stromal lymphoprotein.

1. Brusselle GG. *Nature Med*. 2013;19(8):977-979. **2.** Walford HH. *J Asthma Allergy*. 2014;7:53-65. **3.** Jackson DJ, Johnston SL. *J Allergy Clin Immunol*. 2010;126(5):892-3890. **4.** National Heart, Lung, and Blood Institutes. National Asthma Education and Prevention Program (NAEPP). August 2007.

ICS Withdrawal in Moderate Persistent Asthma

	(n=27)
Age - mean (yrs)	41 ± 14
Male/Female	8/19
Atopy	18
FEV_1 L	2.60 ± 0.83
% pred	106 ± 13
PC_{20} (mg/ml)	1.4 ± 2.0
Met criteria for exacerbation	13 (52)

Castro et al AJRCCM 2004:169:842-849

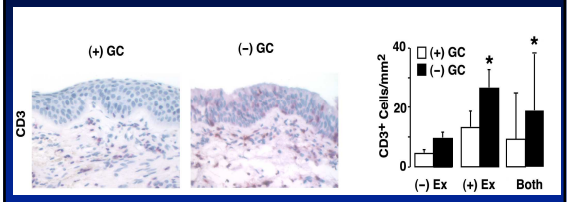
Physiologic Changes With ICS Withdrawal

	No Exacerbation (N=12)		Exacerbation (N=13)	
	(+) GC	(-) GC	(+) GC	(-) GC
AM PEF (L/min)	407 ± 107	389 ± 107†	429 ± 103	374 ± 125†
PM PEF (L/min)	451 ± 125	425 ± 105	424 ± 88	387 ± 125
FEV_1 (L)	2.89 ± 0.83	2.80 ± 0.82	2.91 ± 0.75	2.16 ± 0.99†
% Pred	87 ± 12	84 ± 13	94 ± 13	74 ± 24†
Range	63 - 107	61 - 107	71 - 111	32 - 114
FEV_1 PC_{20} (mg/ml)	3.7 ± 5.8	2.2 ± 4.5	3.4 ± 4.9	1.7 ± 3.5†
Range	0.13 - 16	0.16 - 16	0.05 - 16	0.03 - 12

†Value significantly different (P<0.05) from value for asthma subjects (+) GC.

Castro et al AJRCCM 2004:169:842-849

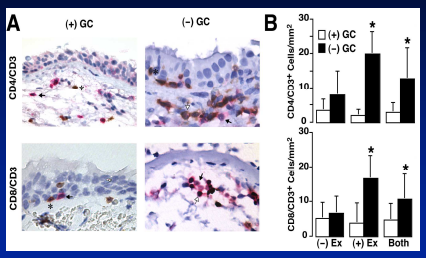
Inflammatory Responses During an Asthma Exacerbation



Corr with increase in β-agonist r = 0.55, p = 0.03 and reactivity r = -0.41, p = 0.04

Castro et al AJRCCM 2004:169:842-849

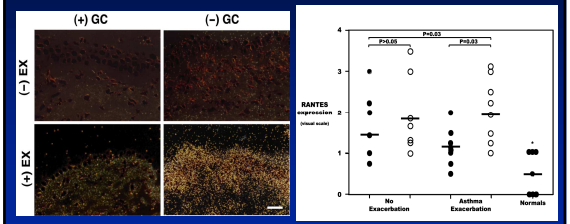
T cell subsets in the Airway During an Asthma Exacerbation



CD8 corr with decrease in FEV_1, r = -0.76, p = 0.02 and reactivity r = -0.66, p = 0.05

Castro et al AJRCCM 2004:169:842-849

RANTES Expression in the Airway Epithelium following Steroid Withdrawal



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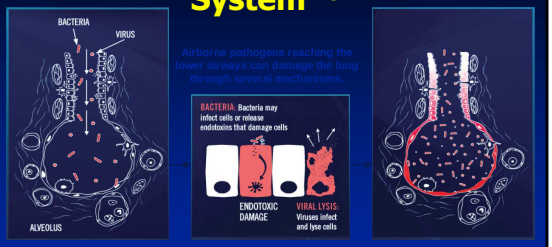
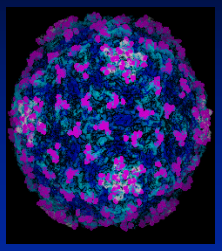
The Role of the Respiratory Immune System[1-3]



1. Sadikot et al. *Am J Respir Crit Care Med.* 2005;171(11):1209-1223.
2. Nalkiri et al. Vaccine. 2008;26(Suppl 4):D50-D60.
3. Curtis JL. *Proc Am Thorac Soc.* 2006;3(5):412-416.

Mechanisms of VRI-Induced Asthma Exacerbations

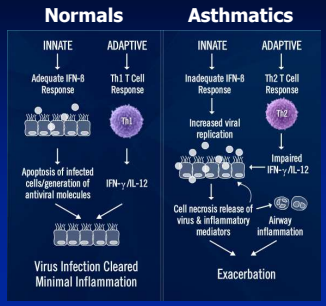
- Viral infections (esp. RV) frequently cause exacerbations of asthma
- Possible mechanisms
  - Extension into the lower airway[1-3]
  - Inflammation with lymphocytes, eosinophils, neutrophils [2,3]



1. Gern JE et al. *Am J Respir Crit Care Med.* 1997;155:1159.
2. Gern JE, Busse WW. *J Allergy Clin Immunol.* 2000;106:201.
3. Fraenkel DJ et al. *Am J Respir Crit Care Med.* 1995;151:879.

Poor Viral Clearance May Also Lead to Exacerbations

- A Th2 bias may also limit the respiratory immune system's ability to effectively clear virus
- This may lead to greater viral replication, lysis of epithelial cells, airway inflammation, and asthma exacerbations[1]

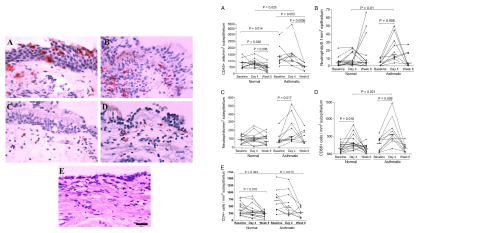


Mallia et al. *Chest.* 2006;130:1203-1210.

CHEST

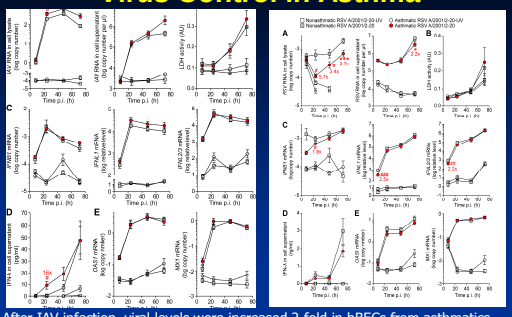
From: Airway Inflammation and Illness Severity in Response to Experimental Rhinovirus Infection in Asthma

Chest. 2014;145(6):1219-1229. doi:10.1378/chest.13-1567



Cell counts in bronchial biopsy specimens of subjects with and without asthma at baseline and days 4 and 6 of rhinovirus 16 infection. A, CD45+ cells. B, Epithelial neutrophils. C, Subepithelial neutrophils. D, CD68+ cells. E, CD4+ cells. Data are presented as the number of positive cells per square millimeter of subepithelium or per 0.1 mm² of epithelium. ▲ and ▲ show individual counts, and horizontal bars show median values (Wilcoxon matched pairs and Mann-Whitney U tests).

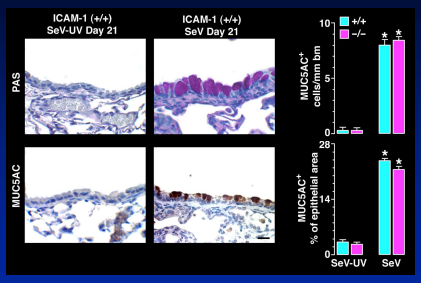
Interferon Response & Respiratory Virus Control in Asthma



After IAV infection, viral levels were increased 2-fold in hBECs from asthmatics compared to controls (P < .05) but not following RSV infection.

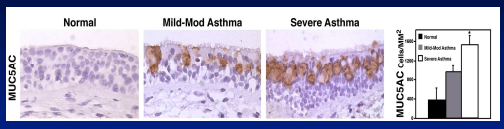
Patel, DA et al JACI 2014; 134(6):1402-1412.

Virus-induced Goblet Cell Hyperplasia



Walter M et al J Clin Invest 2002;110:165-75.

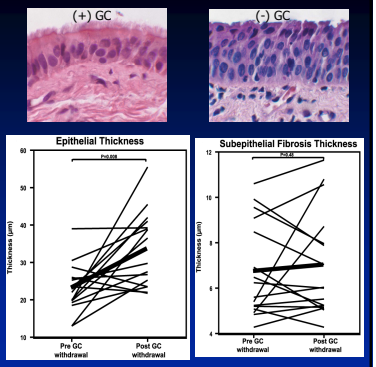
Mucin Products and Goblet Cell Hyperplasia



- **Increase in mucin products have been described in mild- moderate asthma - MUC2, MUC5B, and MUC5AC (Ordonez AJRCCM 2001;163:517)**
- **In severe asthma, there appears to be a marked increase in goblet cells and mucin products as well**

Christie et al PATS 2007:175:A837

Airway Epithelial Remodeling with Steroid Withdrawal



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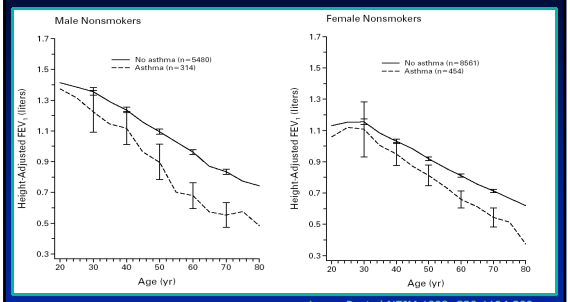
Airway Remodeling in Asthma

- Individuals with asthma have a more rapid decline in FEV_1 with age than normals
- Despite long term therapy with steroids, some asthmatics develop irreversible airflow obstruction and persistent airway hyperreactivity
- Repetitive injury and repair of airways caused by chronic inflammation results in structural changes
- Healing of the airways involves replacement with normal cells or replacement by connective tissue/scar

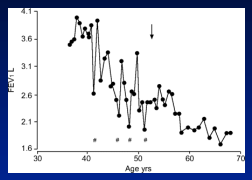
Decline in Lung Function in Asthma
(15 years follow up)



Lange P. et al NEJM 1998; 339:1194-200

Exacerbations -Leads to Remodeling?

- Bai et al. studied 93 asthmatics prospectively for ≥5 yrs (median 11 yrs)
- 60% experienced at least one severe exacerbation*
- Exacerbators experienced greater decline in FEV_1 - difference 16.9 ml/yr
- One exacerbation per yr associated with 30 ml greater decline in FEV_1



*Hospitalization or ≥20% and ≥500 ml drop in FEV1

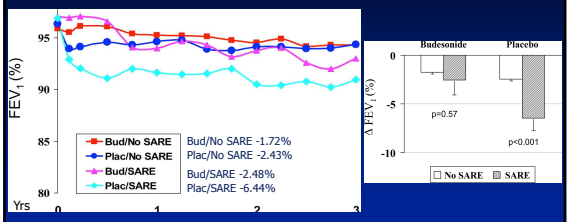
Bai et al ERJ 2007;30:452-6

Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START)

- 7,165 patients (5-66 yo) with persistent asthma <2 yrs randomized to budesonide vs. placebo for 3 yrs
- Mean followup: 2.47 yr Bud; 2.44 yr placebo
- Drop-out rates: 27.5% Bud; 28.6% placebo
- Added ICS: 12.5% Bud; 23.6% placebo

O'Byrne et al AJRCCM 2009;179:19-24

Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START)



- Mean yr decline in FEV_1 in placebo grp with SARE vs w/o: 66 vs 34 ml
- Mean yr decline in FEV_1 in Bud grp with SARE vs w/o: 27 vs 21 ml

O'Byrne et al AJRCCM 2009;179:19-24

Exacerbations and Airway Remodeling

- Viruses are a common cause of asthma exacerbations leading to AHR and GCM
- Exacerbations are associated with the influx of CD4 and CD8 lymphocytes
- Worsening of airway inflammation during exacerbations may accelerate loss of lung function
- ICS may prevent progressive loss of lung function in those with severe exacerbations
- Promising therapy such as biologics and thermoplasty may modify airway remodeling

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