Eastern Allergy Conference:

Role of viral infection in Asthma Exacerbations

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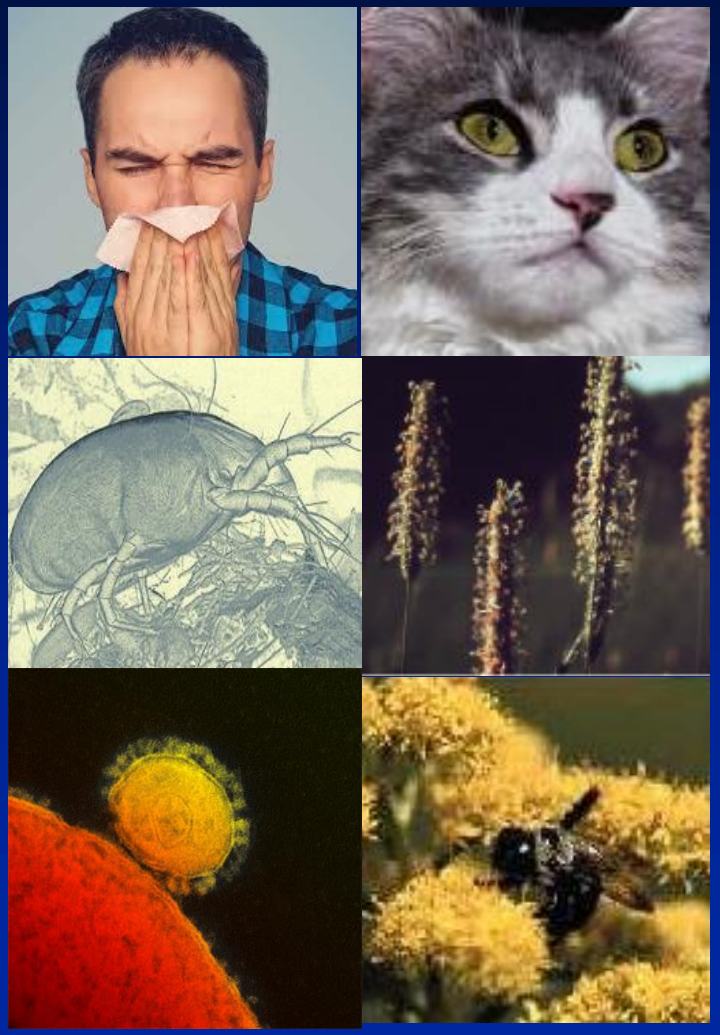
Learning Objectives

On completion of this learning activity, participants should be able to:

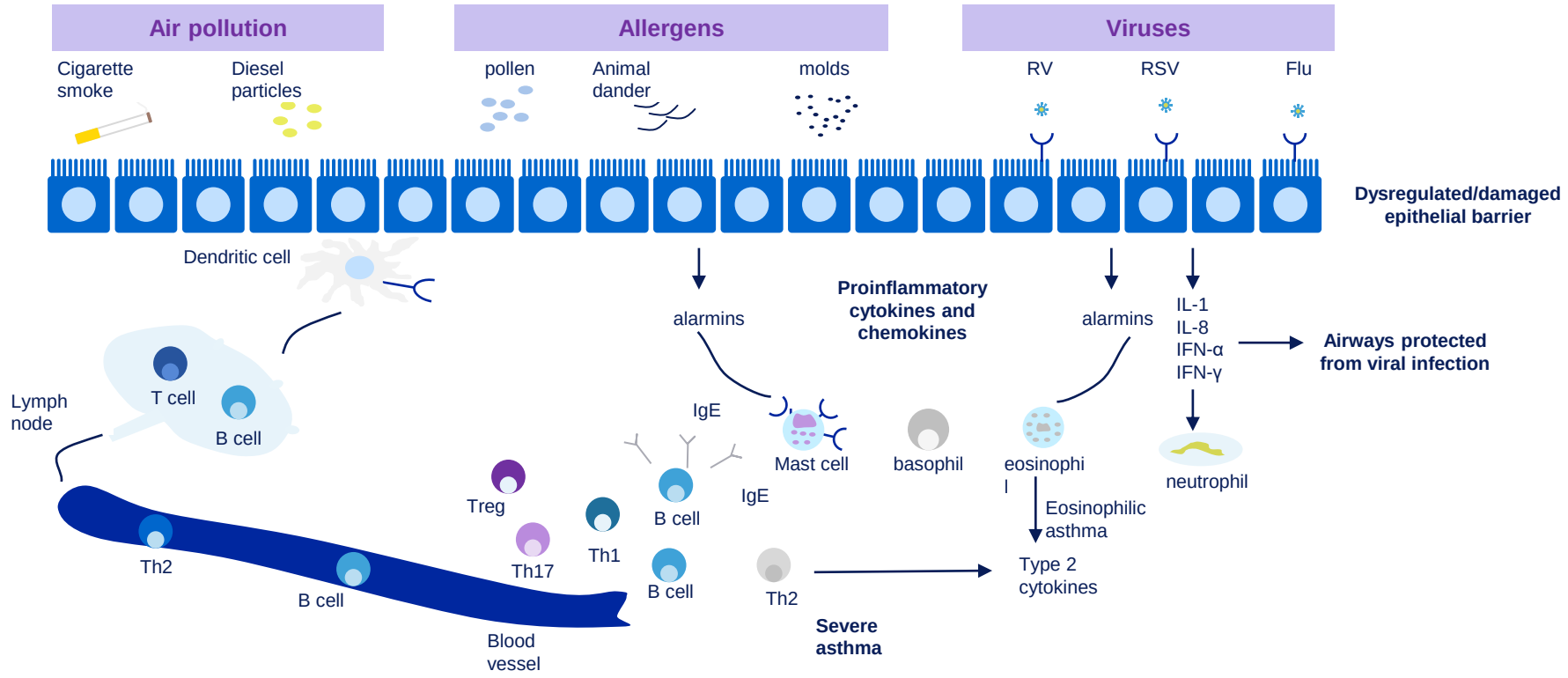
- **Understand the role of viral infection in exacerbations**
- **Describe the potential mechanisms of action of viruses leading to exacerbations**
- **Identify promising agents that can modify response to viral infections**

Causes of Asthma Exacerbations

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

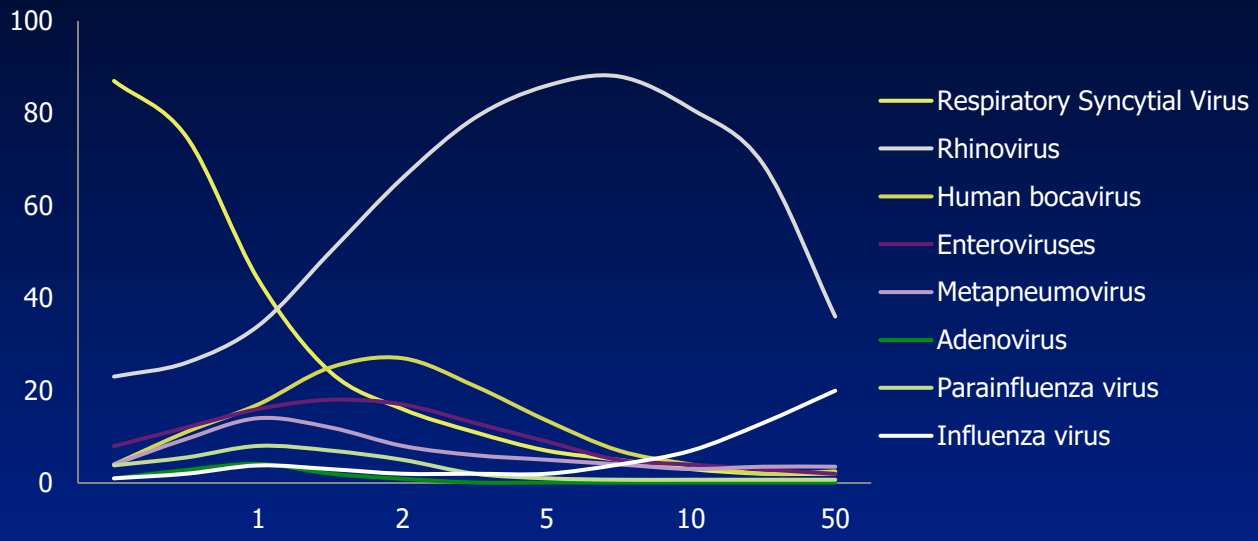


THERE ARE MULTIPLE TRIGGERS FOR ASTHMA EXACERBATIONS



Busse, WW et al. N Engl J Med, 2011;364(11):1005-15. Jartti, T et al. Semin Immunopathol, 2020;42(1):61-74.

Role of viruses in Asthma Exacerbations



- **Viruses cause asthma exacerbations in adults (50-75%) and children (80%)**
- **Most common viruses causing exacerbations: RVs (60%), influenza, RSV (especially infants)…and recently COVID-19**
- **The response to viral infection is shaped by the host's antiviral response**
- **Worsening of airway inflammation during exacerbations may lead to accelerated loss of lung function and structural changes**

Rhinovirus causes the majority of virally-induced asthma exacerbations after one year of age.

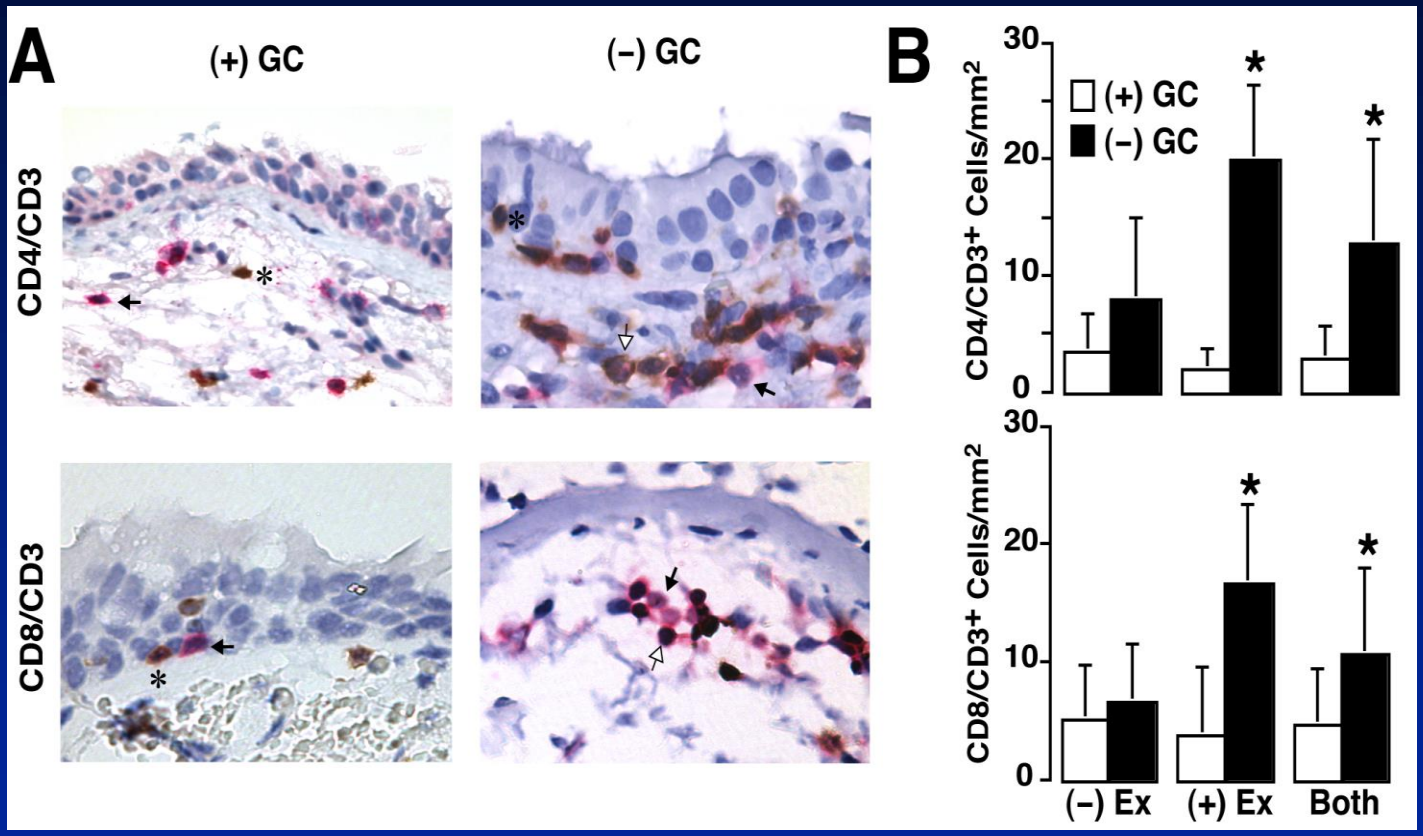
Asthma Exacerbations - Lessons learned from ICS Withdrawal

	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

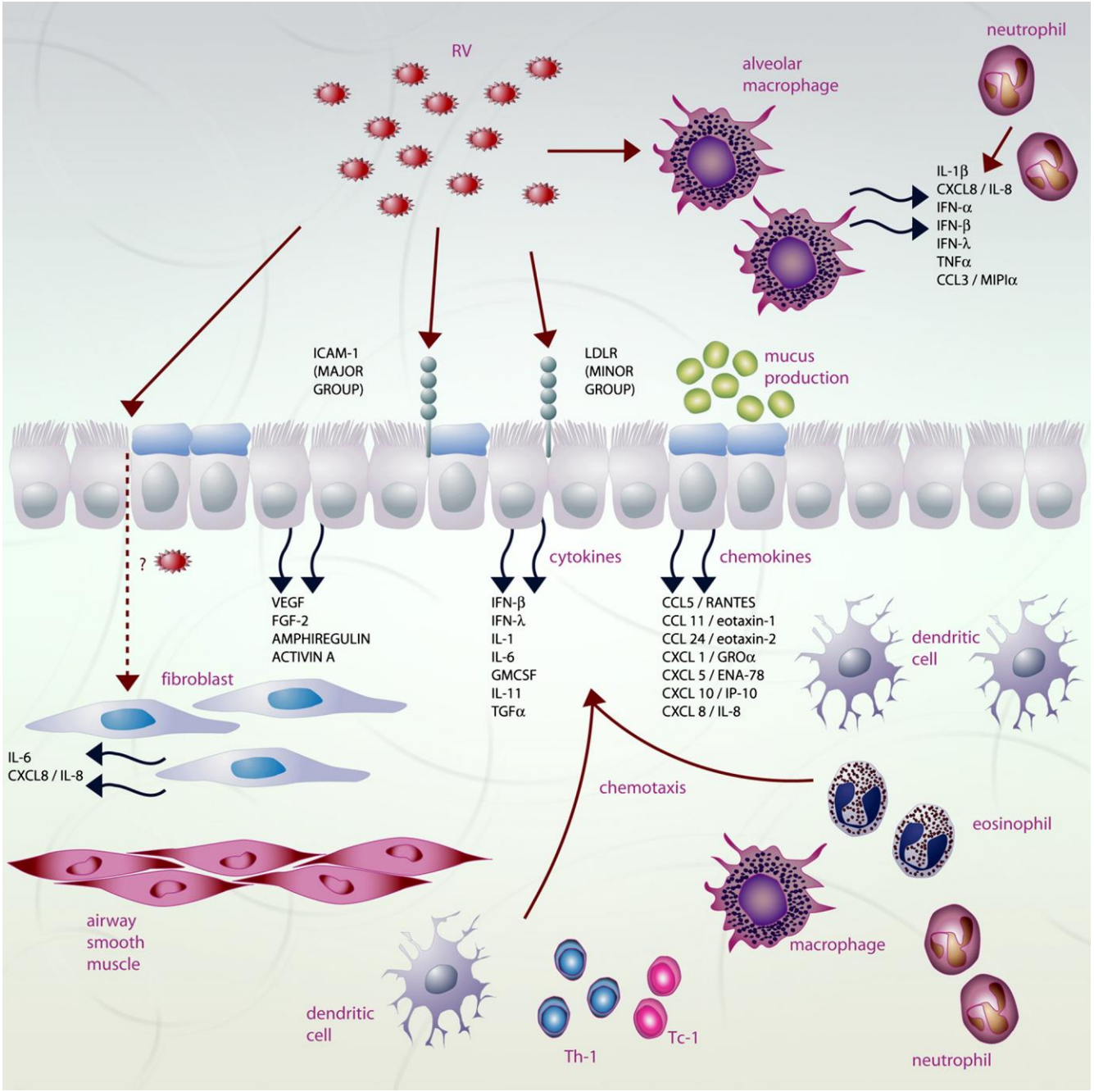
T cell subsets in the Airway During an Asthma Exacerbation



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

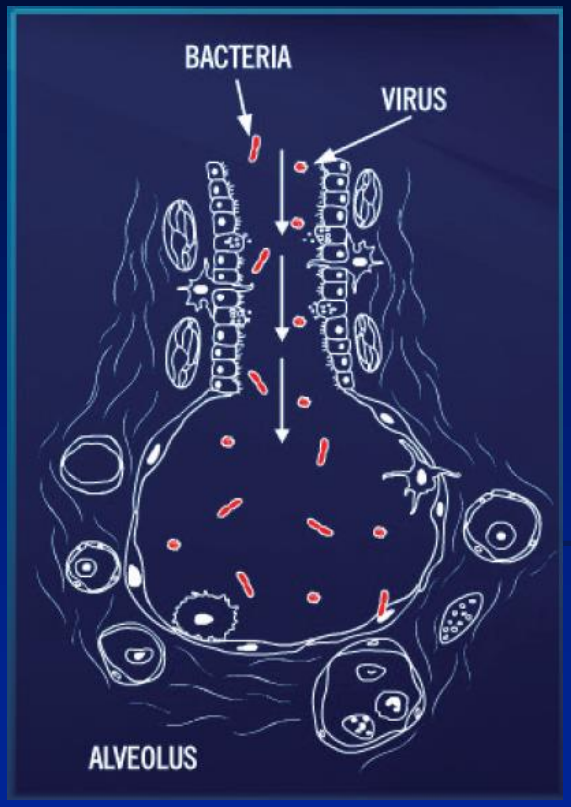
Castro et al AJRCCM 2004:169:842-849

Response to Rhinovirus infection

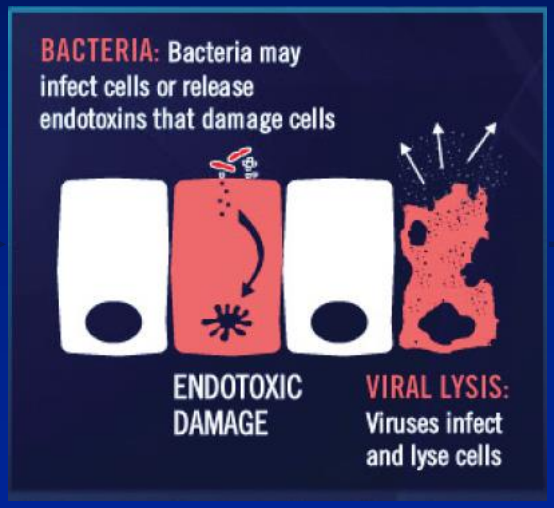


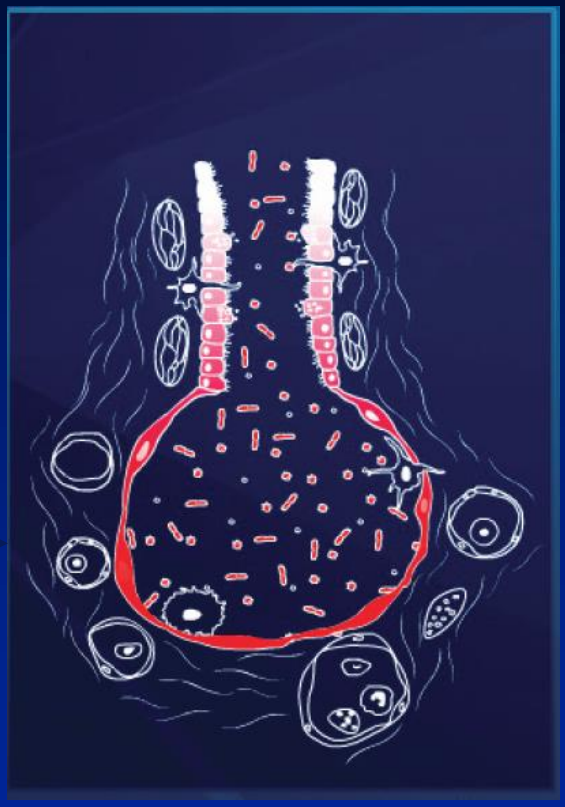
D. Jackson, S. Johnston. Journal of Allergy and Clinical Immunology 2010 125, 1178-1187DOI: (10.1016/j.jaci.2010.04.021)

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



Airborne pathogens reaching the lower airways can damage the lung through several mechanisms.



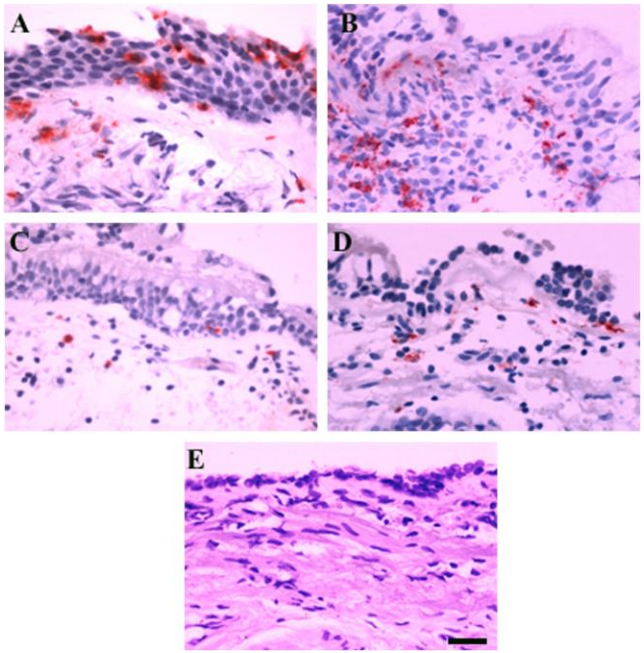


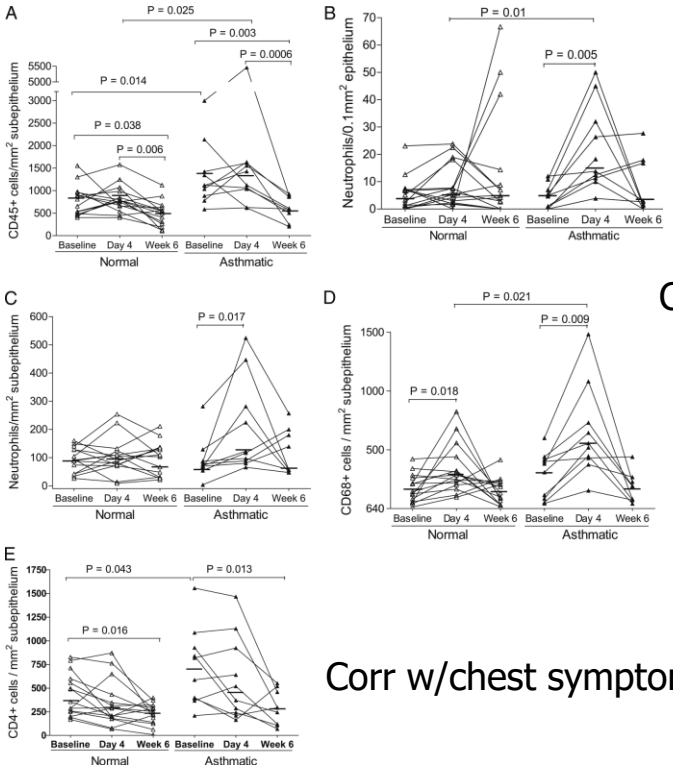
The respiratory immune system identifies and clears pathogens from the airway lumen to prevent disruption of lung function.

1. Sadikot et al. *Am J Respir Crit Care Med*. 2005;171(11):1209-1223.
2. Kuiken et al. *Vaccine*. 2008;26(Suppl 4):D59-D66.
3. Curtis JL. *Proc Am Thorac Soc*. 2005;2(5):412-416.

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

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





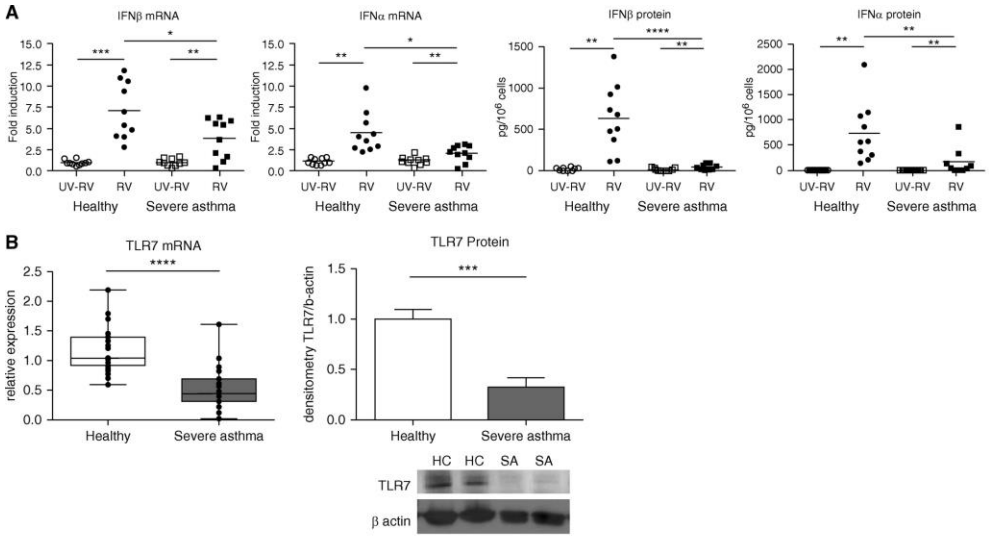
Corr w/viral load

Corr w/chest symptoms scores

Cell counts in bronchial biopsy specimens of subjects with (n=10) and without asthma (n=15) 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 mm^2 of epithelium. △ and ▲ show individual counts, and horizontal bars show median values (Wilcoxon matched pairs and Mann-Whitney U tests).

Interferon Response in Alveolar Macrophages

- TLR7 is significantly reduced in AM in severe asthmatics (n=43) and following RV & Imiquimod c/w healthy subjects (n=44)
- TLR7 inversely correlates with # exacerbations & ACQ



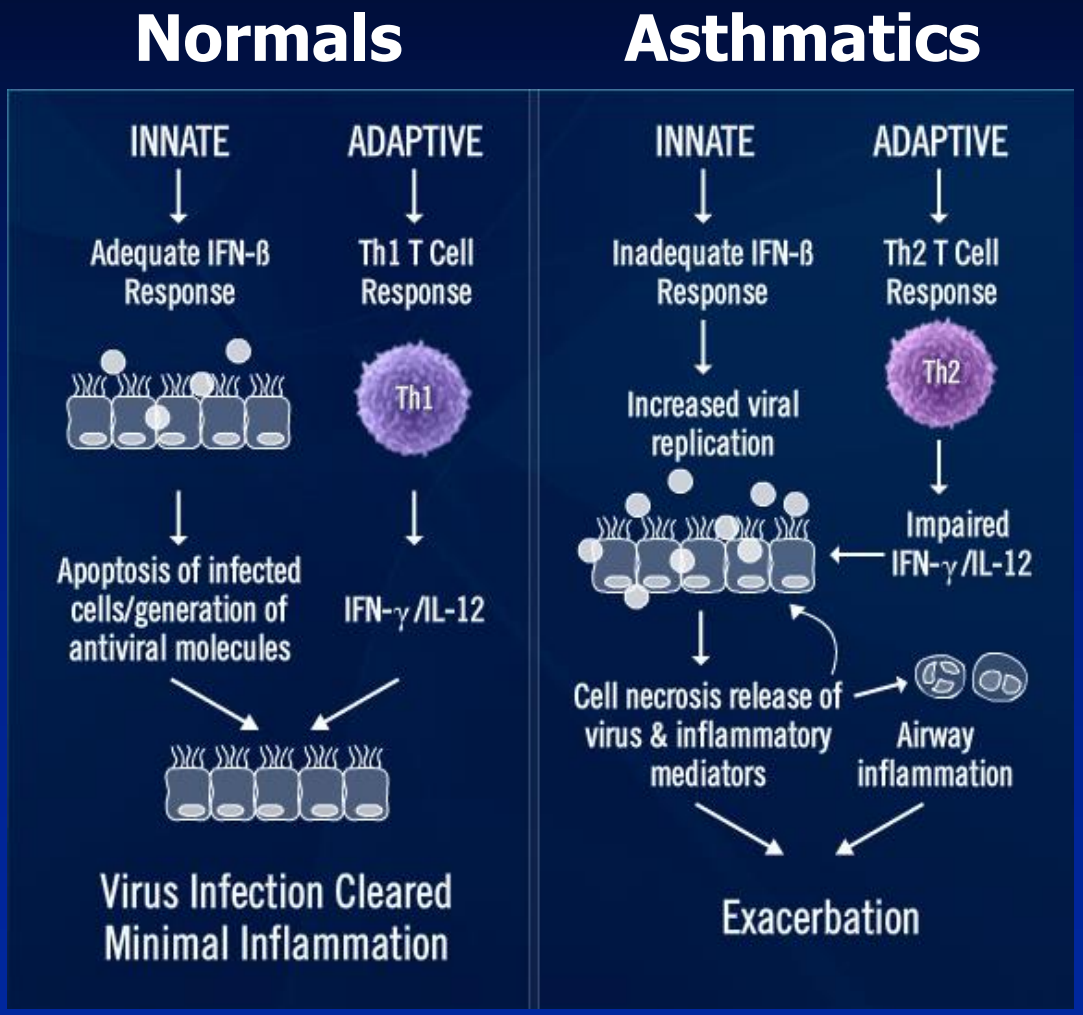
- AM from severe asthmatics have elevated miRNA (-150, -152, -375) which reduce TLR7 expression
- Knockdown of miRNAs increases RV-induced IFN production by AM

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$

Rupani, et al; *Am J Respir Crit Care Med 2016;* 194, 26-37. DOI: 10.1164/rccm.201502-0280OC

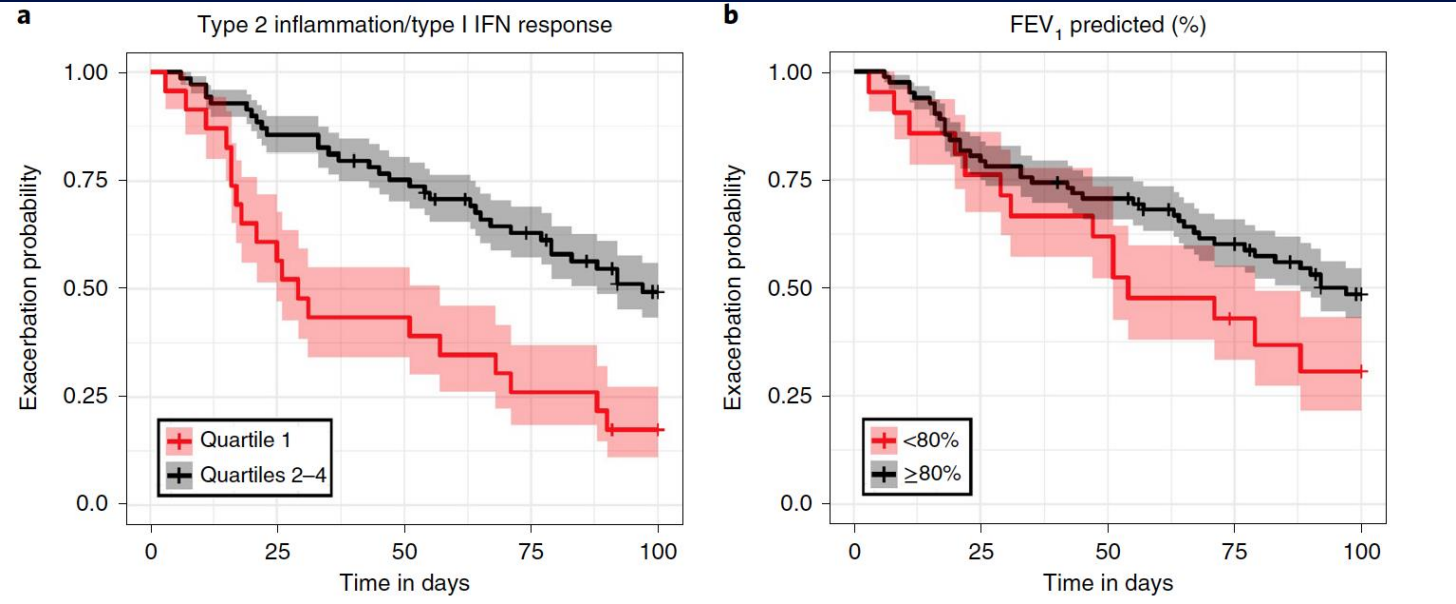
Poor Viral Clearance May Also Lead to Exacerbations

- 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.

Immunopathogenesis of Exacerbations: "Type 2 Inflammation" and "Type I Interferon Response" Predicts Exacerbation Risk

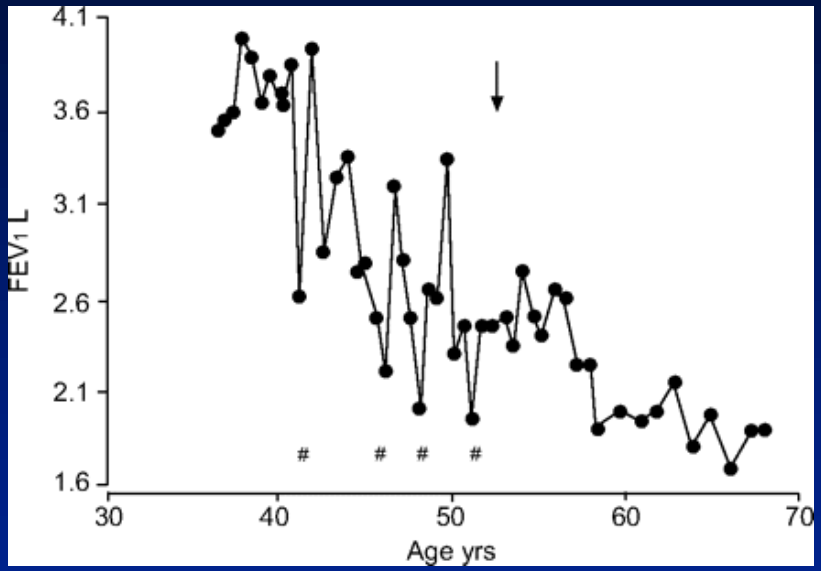


Epithelial SMAD3 signaling is upregulated and lymphocyte response pathways are downregulated early in exacerbation, followed by later upregulation of effector pathways including EGFR signaling, extracellular matrix production, mucus hypersecretion, and eosinophil activation

Altman MC et al. Nature Immunol. 2019

Exacerbations -Leads to Remodeling?

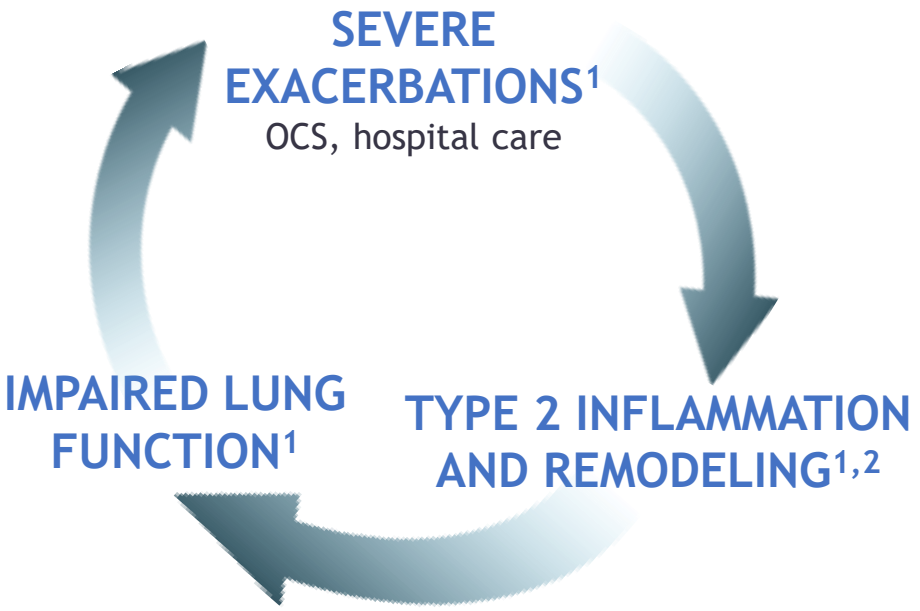
- Bai et al. studied 93 asthmatics prospectively for ≥5 yrs (median 11 yrs)
- 60% experienced at least one severe exacerbation*
- Exacerbators experienced greater decline in FEV_1 - difference 16.9 ml/yr
- One exacerbation per yr associated with 30 ml greater decline in FEV_1

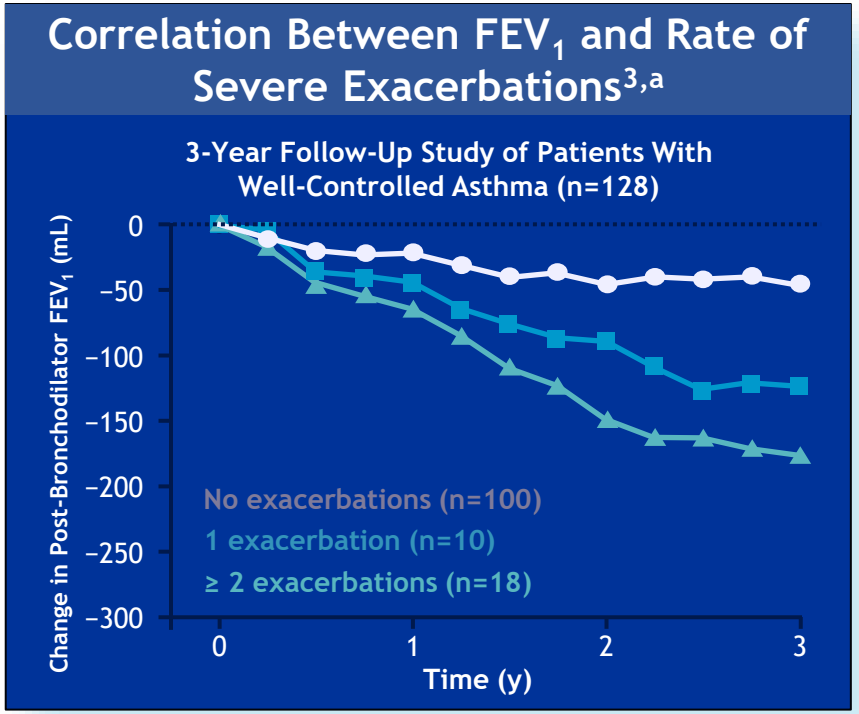


*Hospitalization or ≥20% and ≥500 ml drop in FEV1

Bai et al ERJ 2007;30:452-6

Type 2 Inflammation May Contribute to a Self-Perpetuating Cycle of Impaired Lung Function and Severe Exacerbations



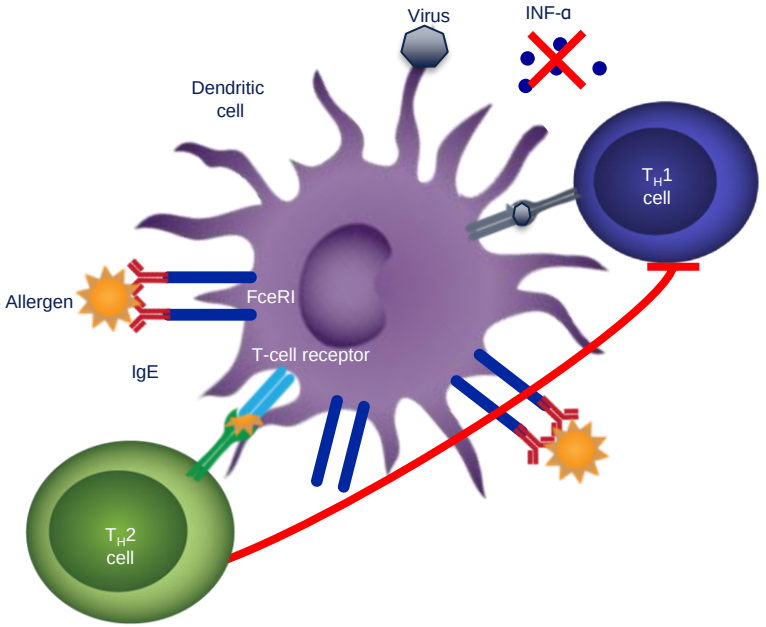


Maria: Significant airflow obstruction FEV1: 1.99 L (60%); post BD:2.07 (+4%); role of repeated exacerbations

1. Dougherty RH, Fahy JV. *Clin Exp Allergy*. 2009;39(2):193-202; 2. Holgate ST. *Immunol Rev*. 2011;242(1):205-219; 3. Matsunga K et al. *J Allergy Clin Immunol*.

IgE MAY IMPAIR ANTI-VIRAL RESPONSE

- Viral infection causes dendritic cells to release IFN-α, which drives the T_H1 inflammation necessary for viral clearance.[2,3]
- In allergic asthma, dendritic cells have increased expression of the IgE receptor, FceRI.[2,3]
- Receptor crosslinking by IgE/antigen facilitates antigen processing, drives T_H2 inflammation and modifies the T_H1 antiviral response[2,3]
- DCs from patients with asthma secrete less IFN-α upon exposure to virus, and secretion is inversely correlated with serum IgE levels.[3]



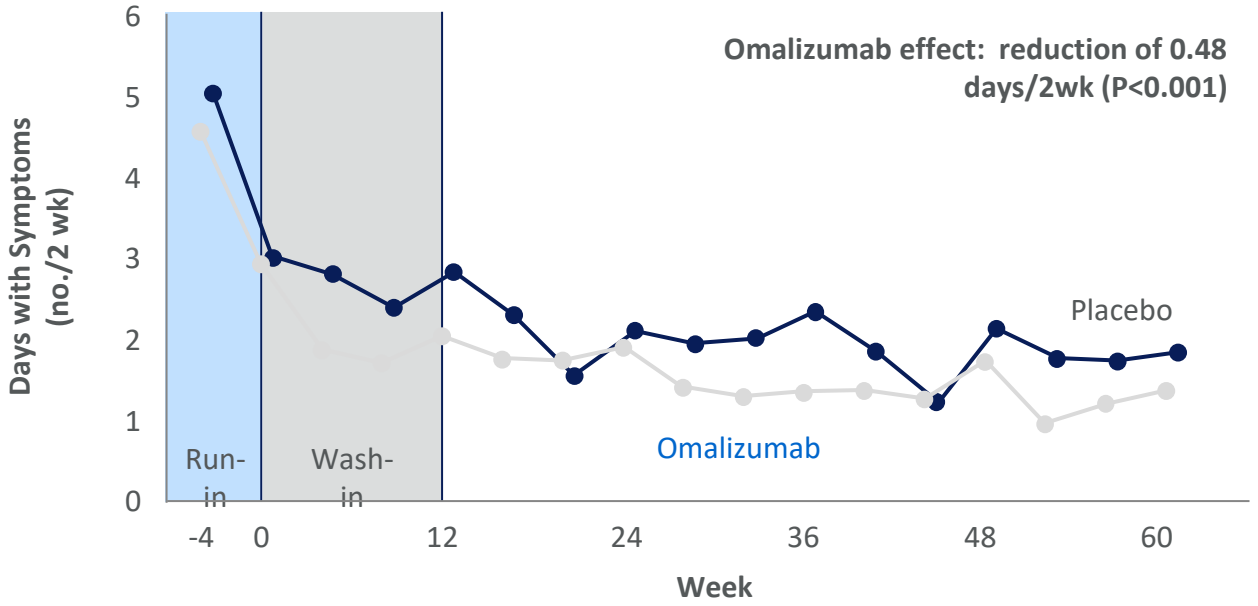
IgE levels are correlated with the severity of viral-induced exacerbations.[4]

1. Figure adapted from Kraft, S and Kinet J-P. *Nat Rev Immunol.* 2007;7(5):365-378. 2. Durrani et al. *J Allergy Clin Immunol.* 2012;130:489-495. 3. Gill MA et al. *J Immunol.* 2010;184:5999–6006. 4. Kantor DB, et al. *J Allergy Clin Immunol* 2016;138:1467-1471 e1469.

Increased Levels of IgE/FcεRI in Allergic Asthma Patients Results in a Decreased Immune Response to Rhinovirus

- **Gill J Immunol 2010**
  - pDCs from patients with asthma secrete less IFN-α upon exposure to influenza A and secretion was inversely correlated with serum IgE levels.
  - IgE cross-linking prior to viral challenge resulted in 1) abrogation of the influenza-induced pDC IFN-α response; 2) diminished influenza and gardiquimod-induced TLR-7 upregulation in pDCs
- **Durrani JACI 2012**
  - After FcεRI cross-linking, allergic asthmatic children had significantly lower HRV-induced IFN responses than allergic nonasthmatic children (IFN-α, $P = .004$; IFN-λ1, $P = .02$) and nonallergic nonasthmatic children (IFN-α, $P = .002$; IFN-λ1, $P = .01$).

The Inner-City Anti-IgE Therapy for Asthma (ICATA)



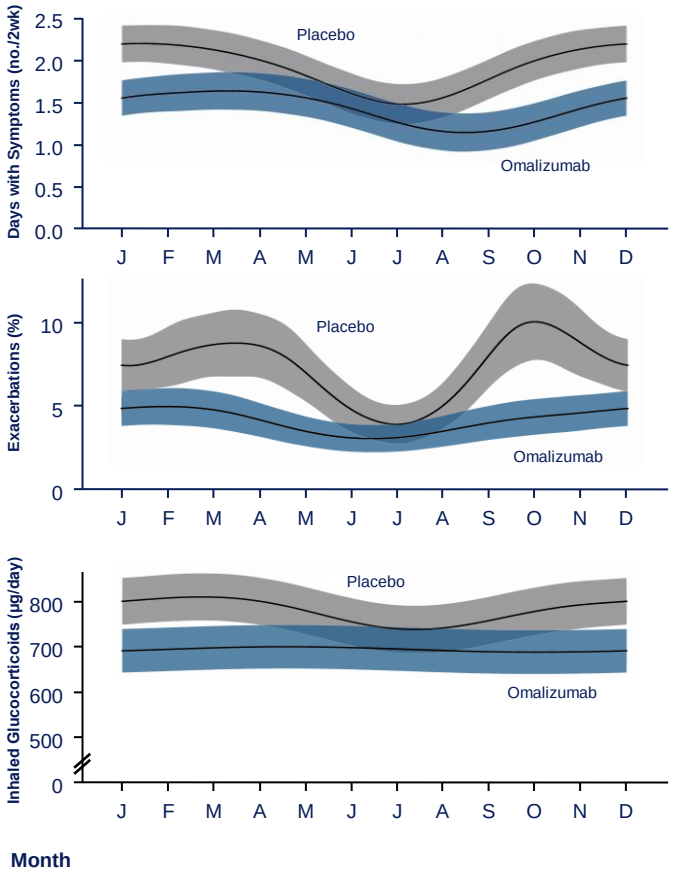
- Exacerbations
  - 48.8% of patients in placebo group vs 30.3% of omalizumab group (P<0.001) experienced exacerbations during study
- Hospitalizations
  - 6.3% of patients in placebo group vs 1.5% of omalizumab group (P = 0.02) were hospitalized because of asthma
- ICS and LABA use lower with omalizumab (P<0.001) and (P=0.003), respectively

Busse WW et al. *N Engl J Med* 2011;364(11):1005-15.

ICATA: Post Hoc Analysis on Seasonal Exacerbations

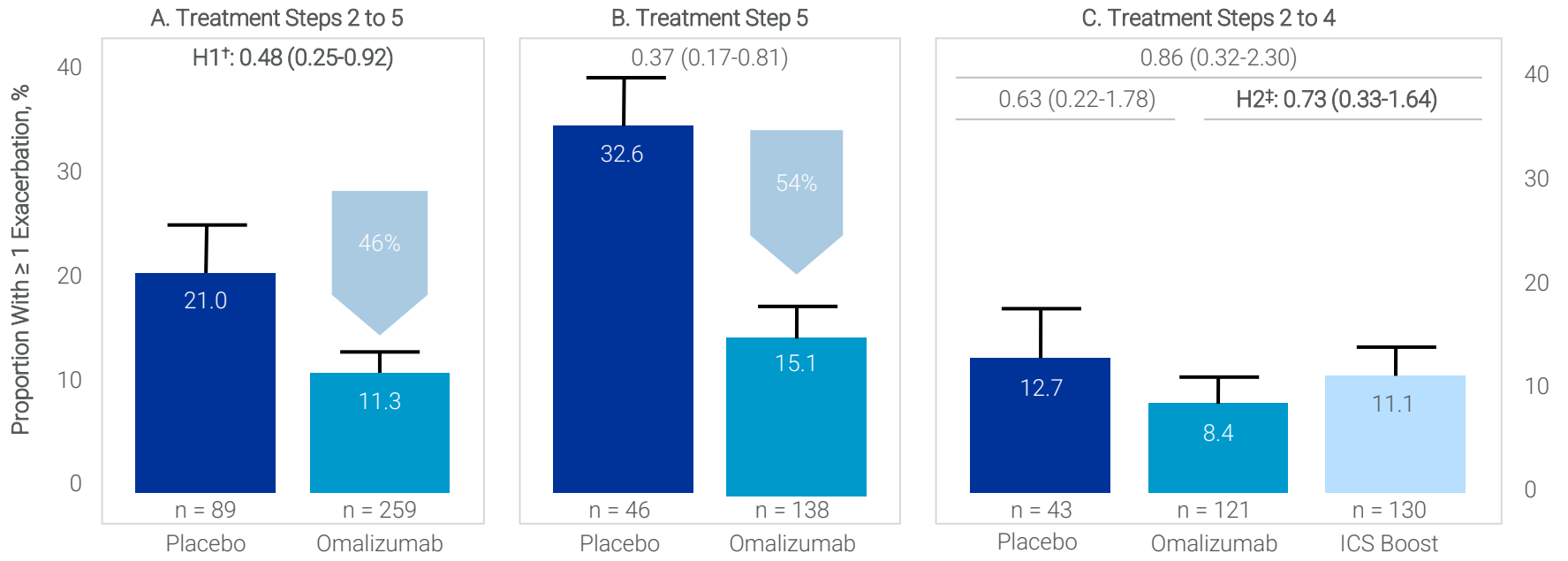
- Omalizumab was associated with reduced exacerbations in the fall and the spring, with or without a viral infection
  - -Average monthly rate of asthma exacerbations nearly doubled in placebo group in fall and spring compared with summer (9.0% and 8.1% vs 4.6%; P<0.001)
  - -Seasonal spike was not observed in omalizumab group (4.3% in fall and 4.2% in spring vs 3.3% in summer)

Band width represents 95% confidence interval



Busse WW et al. *N Engl J Med* 2011;364(11):1005-15.

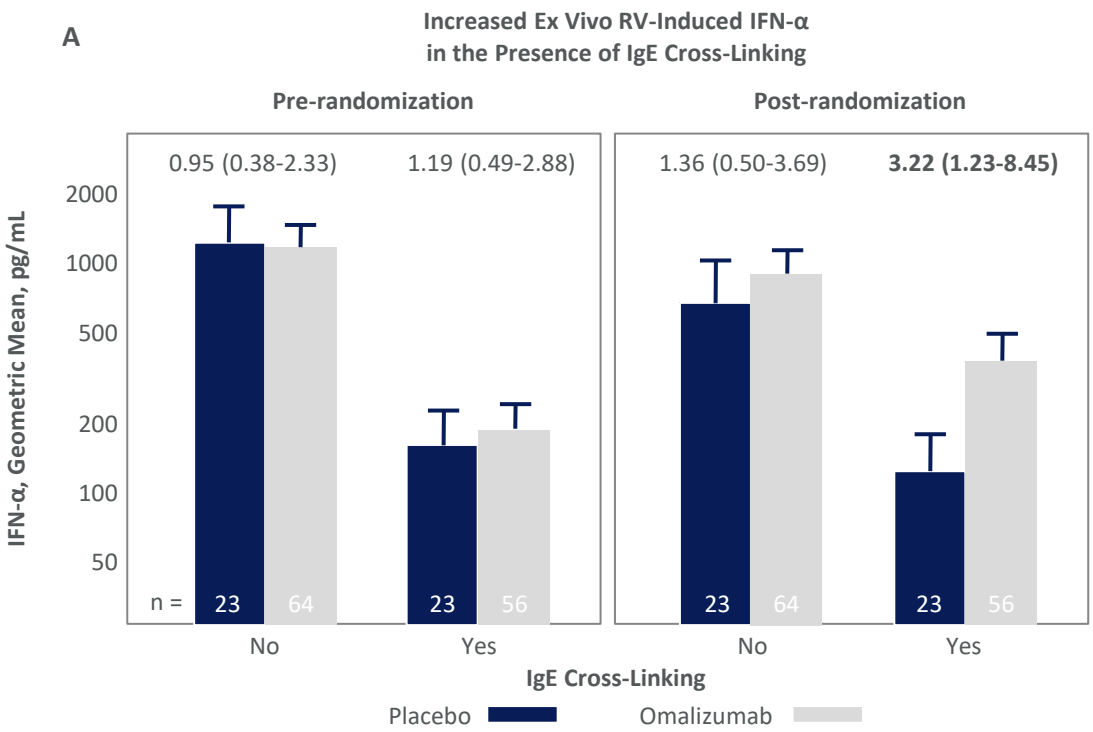
PROSE: Preventative use of anti-IgE

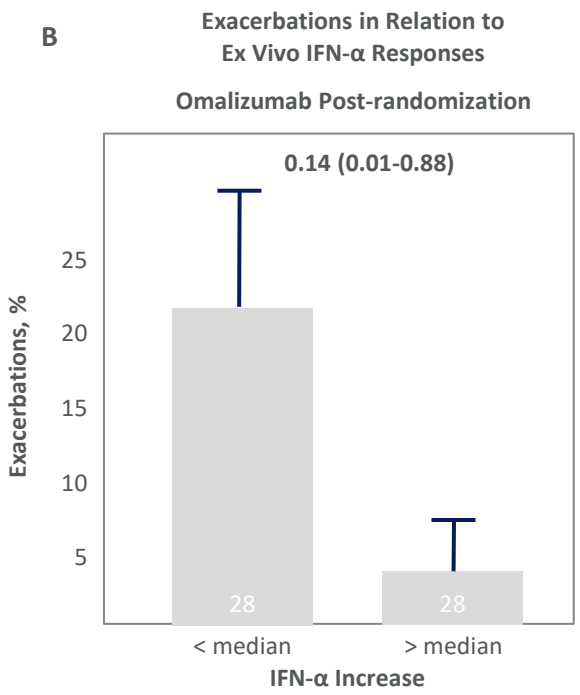


OR, odds ratio.
* Values at the top of each panel are ORs (95% CIs), Exacerbaion defined as need for SCS and/or hospitailzation
†Primary hypothesis 1 (H1): omalizumab is more efficacious than placebo in preventing fall asthma exacerbations.
‡Primary hypothesis 2 (H2): omalizumab is more efficacious than an ICS boost in preventing fall asthma exacerbations.

Teach SJ et al. J Allergy Clin Immunol 2015;136(6):1476-85.

PROSE: PBMC IFN-α augmented by anti-IgE



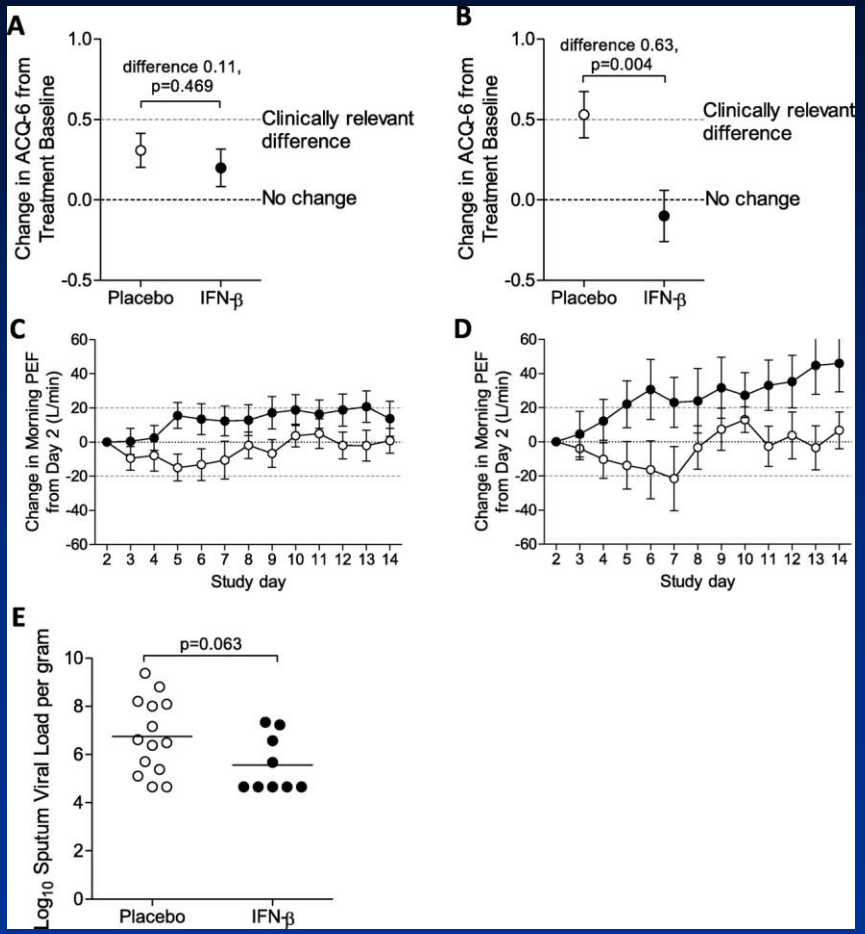


***Values at the top of each panel are ORs (95% CIs).**

Teach SJ et al. *J Allergy Clin Immunol* 2015;136(6):1476-85.

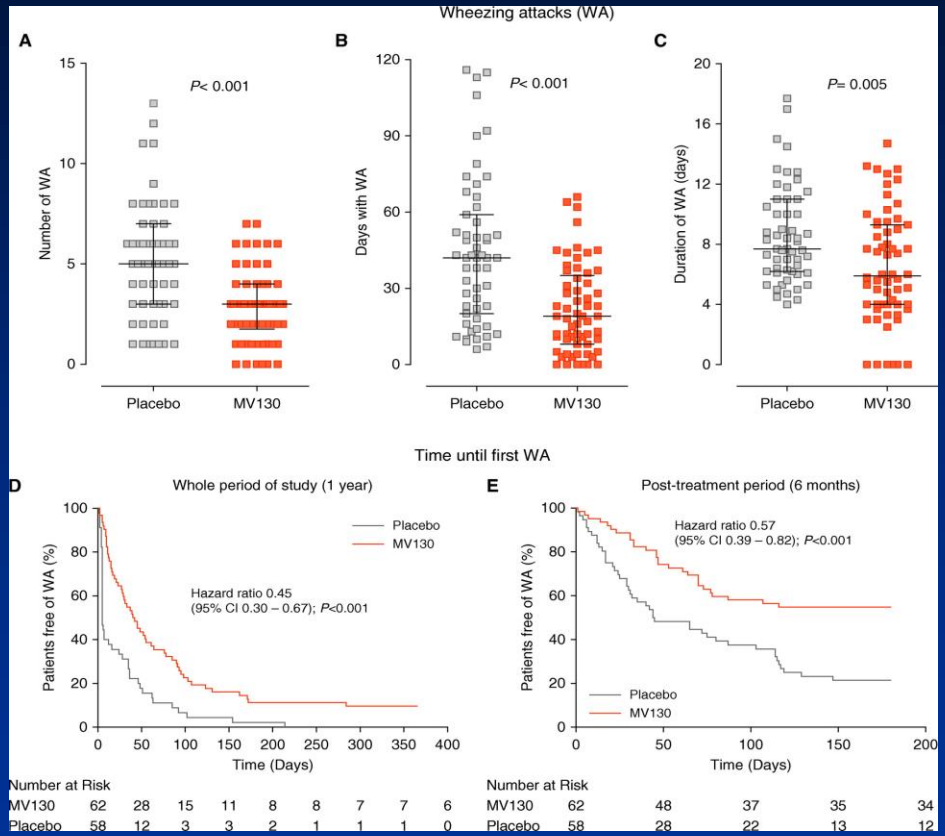
Effect of IFN-β on Asthma Control after Viral Infections

- 147 people with asthma on ICS with a history of virus-associated exacerbations, were randomized to 14-day treatment with inhaled IFN-β (n = 72) or placebo (n = 75) within 24 hours of developing cold symptoms
- IFN-β treatment (n = 58) did not significantly affect the change in ACQ-6 at Day 8 compared with placebo (n = 65).
- Subgroup with difficult-to-treat asthma (BTS Step 4-5) (*B*) showed an increase in ACQ-6 of 0.53 in the placebo group (n = 30) and a decrease of 0.10 in the IFN-β group (n = 24), difference of −0.63 (95% CI −1.05 to −0.21; *P* = 0.004)
- Treatment with IFN-β (*closed symbols*) resulted in faster recovery of morning PEF (*C*), compared with placebo (*open symbols*) measured daily at home (*P* = 0.033; n = 56 for placebo; n = 58 for IFN-β). This improvement was also seen in the British Thoracic Society Step 4-5 (*D*) subgroup
- Sputum (*E*) obtained on Day 4 showed a trend toward reduced rhinovirus load (*P* = 0.063) in IFN-β–treated patients (n = 9) compared with placebo (n = 14)



Ratko Djukanović **et al** *Am J Respir Crit Care Med* 2014; 190145-154. DOI: 10.1164/rccm.201312-2235OC

MV130 Reduced Number and Duration of Wheezing Attacks



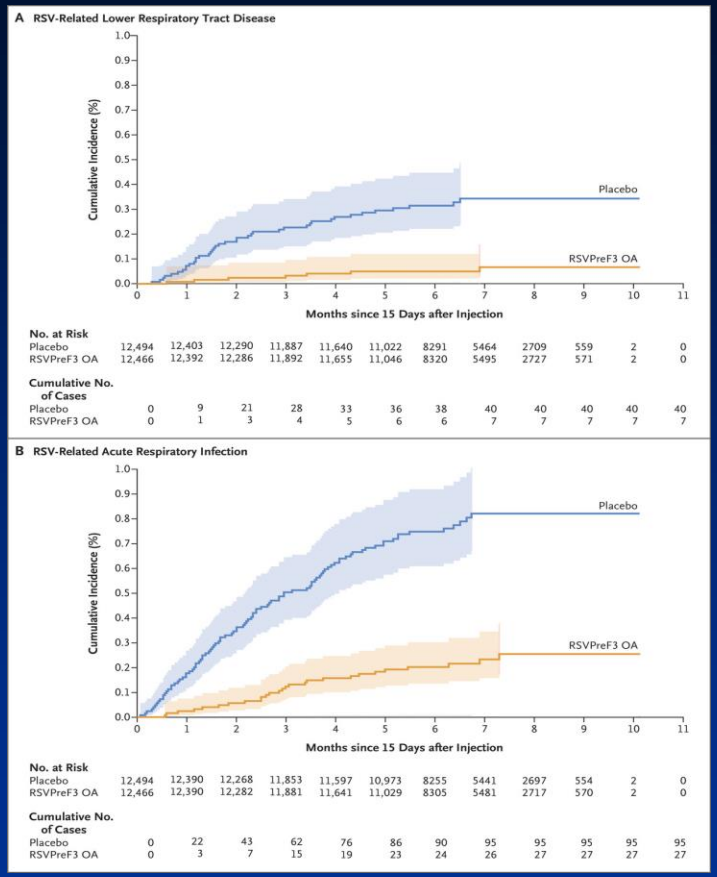
- 120 children <3 yrs old with >3WA during the previous year
- ~40% reduction in wheezing attacks relative to placebo
- Prolonged time to next wheezing attack, including after therapy was discontinued

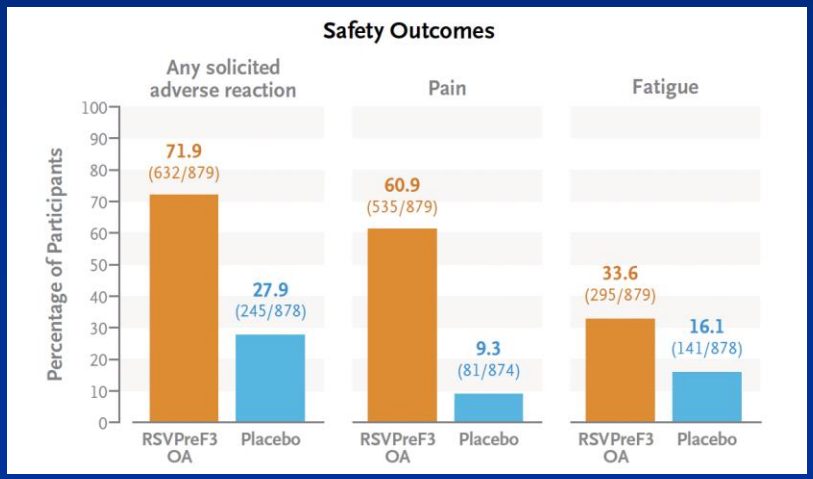
"Mucosal immunotherapy with a sublingual polybacterial preparation (MV130) prevents wheezing episodes in young children and reduces symptoms and medication scores… with a good safety profile"

Nieto A et al. AJRCCM 2021; 204:462-72.

RSV Prefusion F Protein Vaccine in Older Adults

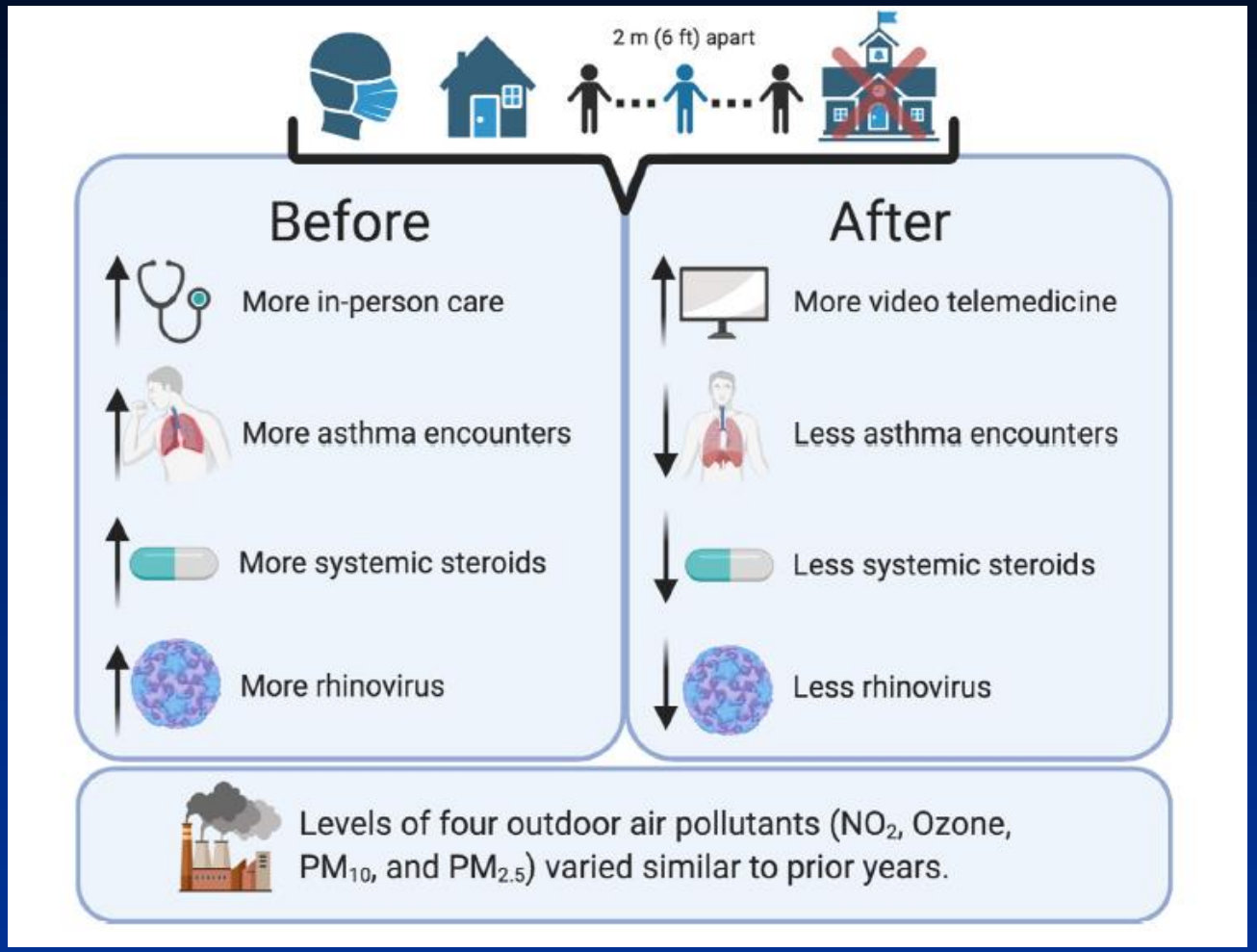
- 25,040 adults ≥60 yrs old in 17 countries assigned to receive a single dose of the RSV Prefusion F3 protein OA vaccine or placebo before the RSV season to show vaccine efficacy against RSV-related lower RTI.
- Vaccine efficacy against RSV-confirmed lower respiratory tract disease was >80% over 6.7 months.





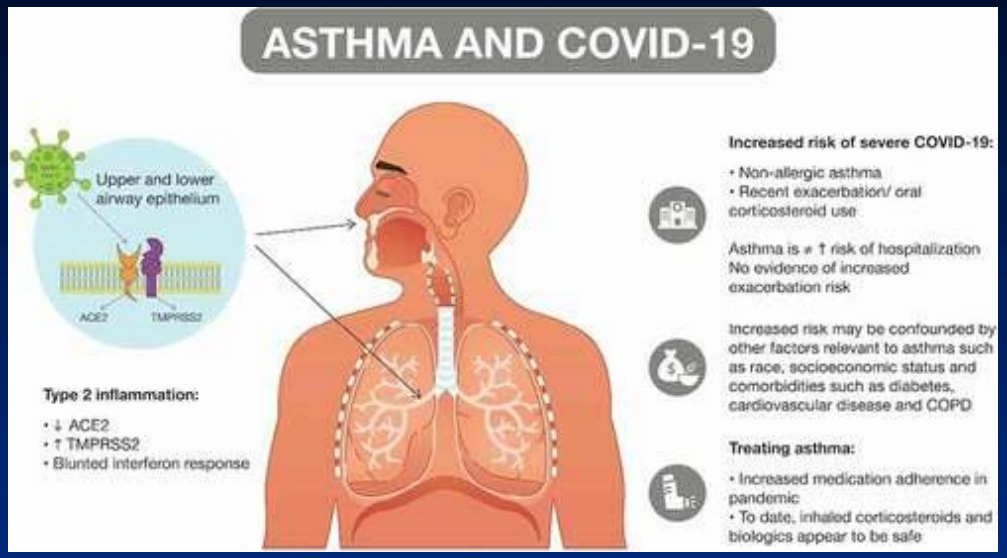
A Papi et al. N Engl J Med 2023;388:595-608.

Impact of COVID-19 Public Health Interventions on Asthma Disease Activity



Taquechel et al, JACI: In Practice 2020

Asthma and COVID-19



- Asthma diagnosis may be a risk factor for severe COVID-19 especially for those with severe disease or nonallergic phenotypes.
- Risk of having COVID-19 was higher in the ones who have interrupted their biological treatment (RR:2.71; 95%CI:1.21-6.06)
- COVID-19 does not appear to provoke asthma exacerbations and asthma therapeutics should be continued for patients with exposure to COVID-19.

Tuncay G et al J Asthma Nov 2021
Howell D et al Expert Rev Respir Med. 2021 Nov;15(11):1377-1386.

Circling Back to Maria

- 12-year-old Latinx junior high school student with coughing and wheezing since early childhood when she experienced RSV and pneumonia
- **Frequent URIs precipitating worsening** of cough and wheezing.
- After addressing her environment…consideration of biologic:
  - Omalizumab would be reasonable given allergic sensitization, strong environmental triggers and recurrent viral URIs
  - Dupilumab, anti-IL5/R or anti-TSLP would be reasonable given T2 driven inflammation (EOS 290, FeNO 87) and significant airflow obstruction for a 12 year old

Role of Viral Infections in Asthma Exacerbations

- Viruses are a common cause of asthma exacerbations leading to AHR and GCM
- Exacerbations are associated with the influx of CD4 and CD8 lymphocytes
- TLR & Type I IFN response appears blunted in asthma
- Receptor crosslinking by IgE modifies the T-1 response to viruses & enhances T-2 inflammation
- Anti-IgE therapy enhances IFNα response and decreases viral-induced exacerbations
- New vaccines against COVID-19 and RSV are now available

…Promising therapy such as biologics and immune modifiers may modify response to viral infections

University of Kansas
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- Victoria Dorman
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- John McClean RRT
- Dylan Pelland
- Jamie Quigley RRT
- Cruise Smyth

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- Alex Alsup MS
- Jianghua He PhD

Radiology
- William Brooks PhD

Laboratory
- Jonathan Boomer PhD
- James Krings MD (WU)
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