

Management of Severe Asthma

Targeted therapy of bronchitis

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Objectives

- Define severe asthma
- Illustrate a “translational approach to management”
- Targeted therapy of bronchitis
- Share our clinical experience

Disclosure

I do not believe that I have any conflicts of interest with this presentation

I have received grants from GlaxoSmithKline, Schering Plough and Pulmatrix Inc for investigator-initiated studies.

I am listed on a patent for a “sputum filtration device”

Our research group is pursuing an IP for a novel “eosinophil biomarker”

I have not provided consultancy or served on the advisory boards of any companies with respiratory products or technologies



November 20, 1938 - June 15, 2011

Definition of Severe Asthma

Major Characteristics

- Oral corticosteroids ($\geq 50\%$ of year)
- High-dose inhaled corticosteroids eg budesonide $>1200 >6$ puffs

Minor Characteristics

- Daily treatment with a controller medication
- Short-acting β -agonist use on a daily or near daily basis
- Persistent airway obstruction
- One or more urgent care visits for asthma per year
- Three or more oral steroid “bursts” per year
- Prompt deterioration with $\leq 25\%$ reduction in oral or ICS
- Near-fatal asthma event in the past

Moore et al, J Allergy Clin Immunol 2007; 119: 405-13.

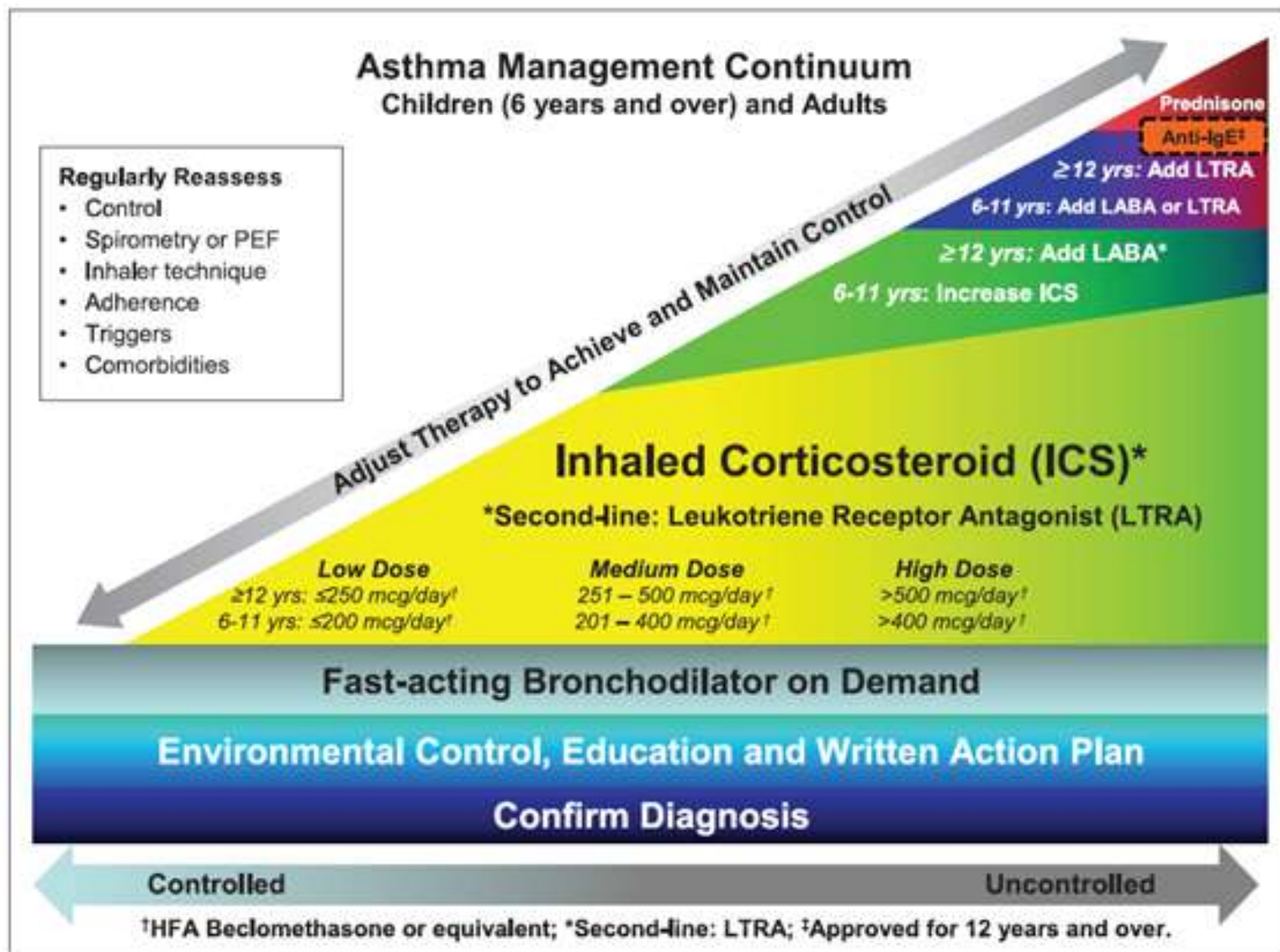
Definition of Severe Asthma

WHO consultation on severe asthma

“Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children).”

Bousquet et al, J Allergy Clin Immunol 2010; 126: 926-38.

Our national guidelines



Large asthma trials that influence guidelines

FACET: add LABA to mod dose of ICS (N Engl J Med 1997;337:1405-11)

OPTIMA: add LABA to low dose of ICS (Am J Respir Crit Care Med 2001;164:1392-7).

START: ICS for all (Lancet 2003;361:1071-6).

RELIEF: LABA prn (Eur Respir J 2003;22:787-94)

GOAL: ICS+LABA long term (Am J Respir Crit Care Med 2004;170:836-44)

SiT: STEAM, STEP, STAY, SMILE: ICS+LABA maintenance and prn (Am J Respir Crit Care Med 2005; 171:129-36; Lancet 2006; 368:744-53)

TALC: Tiotropium (N Engl J Med 2010; 363: 1715-26; J Allergy Clin Immunol 2011; 128: 308-14)

Case history -1

74, female

Never smoked, non-atopic, no CAD

Previous PC₂₀ 4.2 mg/ml

FEV₁ 70% predicted, VC 72% predicted, FEV₁/VC 76%

SOBOE despite budesonide 200 + formoterol 12, 3 puffs bid, prednisone 30 mg x 5 days

Referred for pre-op evaluation before parotidectomy



Case history -1

What would you do for this patient?

- 1) Switch to another ICS + LABA
- 2) Add prednisone
- 3) Add Leukotriene antagonist
- 4) Add Tiotropium
- 5) Further evaluation including cardiac

Case history -2

- 23 female, wheezing, sinusitis, abdominal pain
- 8 ER visits, 3 hospitalizations in 1.5 years
- FEV1 1.4L (50%), FEV1/VC 60%, 14% reversibility
- Skin prick test +ve grass, HDM
- Blood eos $7.74 \times 10^9/L$
- Parasite, Coeliac, Vasculitis screen negative
- Serum B₁₂ elevated, Serum IgE: 4081
- FEV1 after 35 mg prednisone 2.4L
- Currently on 20 mg prednisone, fluticasone 500 bid, Salmeterol 50 bid, montelukast 10 mg, salbutamol 8 puffs daily

Chronic Hyperplastic Rhinosinusitis



Case history -2

What would you do for this patient?

- 1) More prednisone
- 2) Add Omalizumab
- 3) Increase ICS + LABA
- 4) Add Tiotropium
- 5) Further evaluation

Case history -3

- 19 yr male, previously well
- Sinusitis after an innocuous upper respiratory infection
- Wheezing, cough, yellow sputum, pulmonary infiltrates
- Mononeuritis
- 6 unscheduled specialist visits, 2 hospitalizations
- Negative skin prick tests, serum IgE 110
- FEV1 1.6L (55%), FEV1/VC 60%, 18% reversibility
- BAL 8% eosinophils, blood 3.2
- Negative vasculitis, parasite screen
- Negative bone marrow
- 24 mg daily medrol + 2G fluticsone + 100 mcg salmeterol
- Significant adverse effects

Case history -3

What would you do for this patient?

- 1) More prednisone
- 2) Antibiotics
- 3) Add montelukast
- 4) Sinus surgery
- 5) Combination of above

Case history -4

- 38 male, asthma since infancy, wheezy bronchitis
- No history to suggest congenital lung diseases
- Non-atopic, Never smoked
- At least 25 ER/unscheduled specialist visits
- Investigations negative for vasculitis, HES, normal AAT, immune deficiencies
- FEV₁/VC 1.9/2.5 (pred. 2.7/3.4, ratio 77%)
- Prednisone 50 mg courses monthly, Symbicort 12 puffs Singulair, Uniphyl
- FEV₁/VC 2.4L (55%)/5.3 (97%), ratio 46%
- No bronchodilator reversibility
- Flow-volume curve suggest mild tracheo-bronchomalacia

Case history -4

What would you do for this patient?

- 1) Decrease prednisone
- 2) Regular maintenance antibiotics
- 3) Add tiotropium
- 4) All of the above
- 5) None of the above

Case history -5

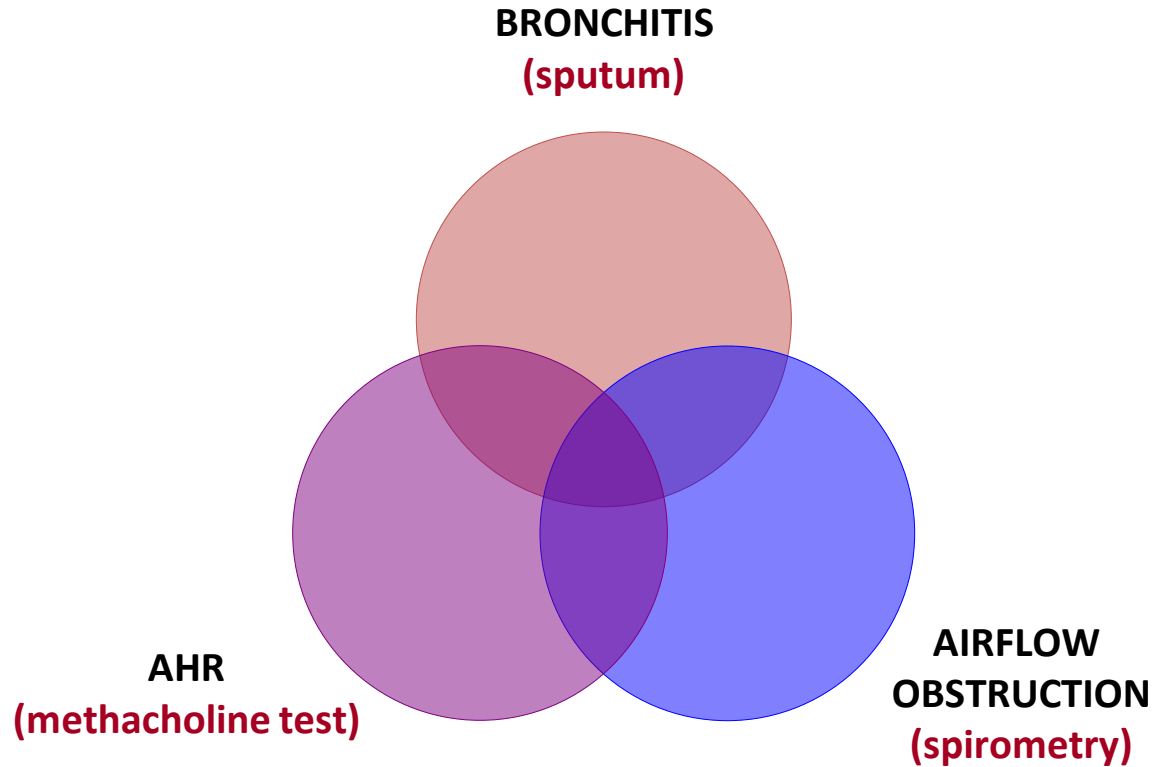
- 45 female, 8-10 puffs of salbutamol daily
- Non-Atopic, never smoked
- Alport's disease, Renal transplant
- Leiomyomas of esophagus (esophagectomy), vulva (hysterectomy)
- FEV₁/VC 1.5/3.5 (pred. 2.9/3.5, ratio 44%), 16% reversibility, PC₂₀ not checked
- RV 170%, TLC 140%, KCO 81%, resistance 11 Raw
- Sputum TCC 6.3, N 35.3%, E 0.6%, M 61.3%, L 2.8%
- Fluticasone +salmeterol 500 bid, montelukast 10 mg, prednisone 5 mg, Cellcept 250 bid theophylline 200 mg

Case history -5

What would you do for this patient?

- 1) More prednisone
- 2) Another immunosuppressant
- 3) Add tiotropium
- 4) No change to current treatment
- 5) Bronchial thermoplasty

Components of Asthma



Sputum cell counts in healthy adults

	Mean	2SD	Median	90th centile
TCC 10 ⁶ /g	4.1	13.8	2.4	9.7
Eosinophils (%)	0.4	2.2	0.0	1.1
Neutrophils (%)	37.5	77.7	36.7	64.4
Macrophages (%)	58.8	100	60.8	86.1

Causes of eosinophilic bronchitis

- Non compliance
- On-going allergen exposure
- Inadequate steroid dose
- Parasitic infestation
- Chronic rhinosinusitis
- Vasculitis
- Chronic eosinophilic pneumonia
- Hypereosinophilic syndrome

Investigation of eosinophilic bronchitis

- Skin tests, IgE
- Vasculitis work up
- Stool examination
- Fungal precipitins
- CT scan chest and sinus
- Evaluation of HES
- T-cell receptor derangements, bone marrow
- Serum tryptase, PDGFR mutation
- T cell cytokines
- Steroid pharmacokinetics

Causes of neutrophilic bronchitis

- Viral infections
- Non-bacterial infections
- Bacterial infections
 - Immune deficiencies
 - Cystic fibrosis
 - bronchiectasis
- Cigarette smoking
- Pollutants
- Occupational exposure
- Inflammatory bowel disorders
- Chronic aspiration

Investigation of neutrophilic bronchitis

- Sputum culture: routine, NTM
- PCR, serology for chlamydia
- T-RFLP, 16S sequencing
- CF screen
- Immune deficiency workup
- Neutrophil function
- CT chest, sinus
- Ciliary motility studies
- Occupational history, endotoxin assay
- Inflammatory bowel disorder screen
- Swallowing assessment

Case history -1

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Never smoked, non-atopic

Previous PC₂₀ 4.2 mg/ml

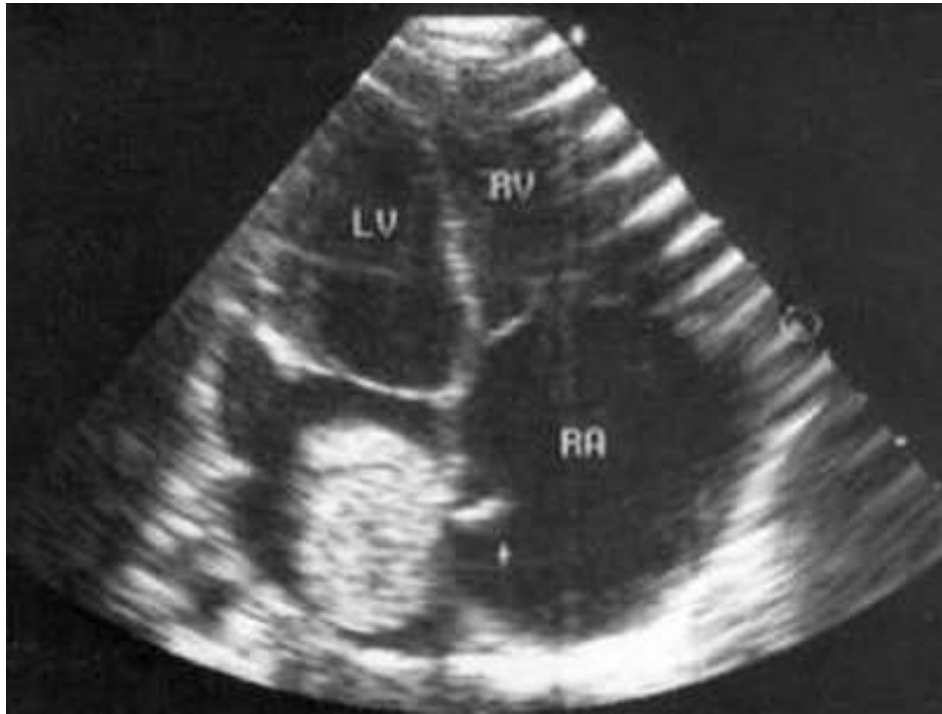
FEV₁ 70% predicted, VC 72% predicted, FEV₁/VC 76%

SOBOE despite budesonide 200 + formoterol 12, 3 puffs bid, prednisone 30 mg x 5 days

Referred for pre-op evaluation before parotidectomy

PC₂₀ methacholine 6.8 mg/ml

Sputum cell counts normal



Consider alternate diagnosis

Poor compliance

Poor inhaler technique

Vocal cord dysfunction

Hyperventilation

On-going allergen exposure

Alternate causes for COPD, eg BO, AAT

Poor steroid absorption

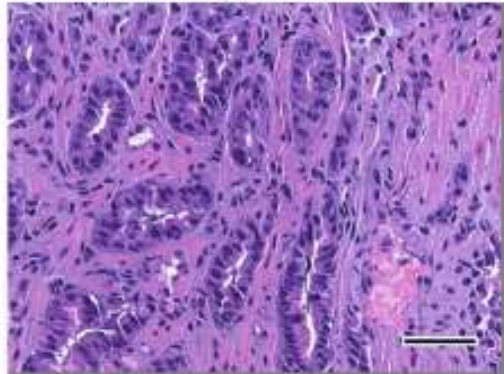
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- Blood eos $7.74 \times 10^9/L$, Sputum eos 20%
- Parasite, Coeliac, Vasculitis screen negative
- Serum B₁₂ elevated, Serum IgE: 4081, normal tryptase
- Bone marrow: no leukemia/lymphoma
- PDGF-FIP1LI, c-kit, abl-bcr mutation absent
- TCR rearrangements not detected
- Serum TARC 360 pg/ml, Sputum IL-5 220 pg/ml
- FEV1 after 35 mg prednisone 2.4L

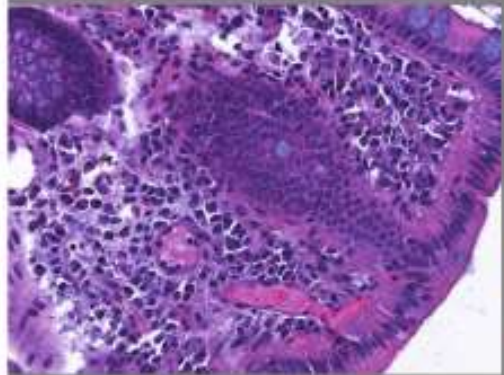
Eosinophilic gastroenteritis

Hematoxylin - Eosin

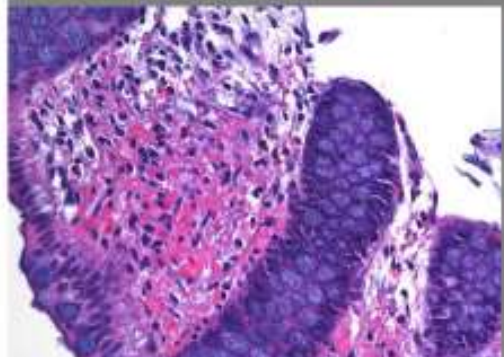
Gastric Antrum



Cecum



Colon



Conventional and non-conventional treatments

- Inhaled, ingested, intravenous corticosteroids
- Hydroxyurea
- Interferon alpha-2B
- Imatinib (Gleevec)
- Cyclophosphamide
- Methotrexate
- Cyclosporine
- Omalizumab
- Alemtuzumab (Campath)
- Sirolimus
- Mycophenolate

Treatment of persistent eosinophilia



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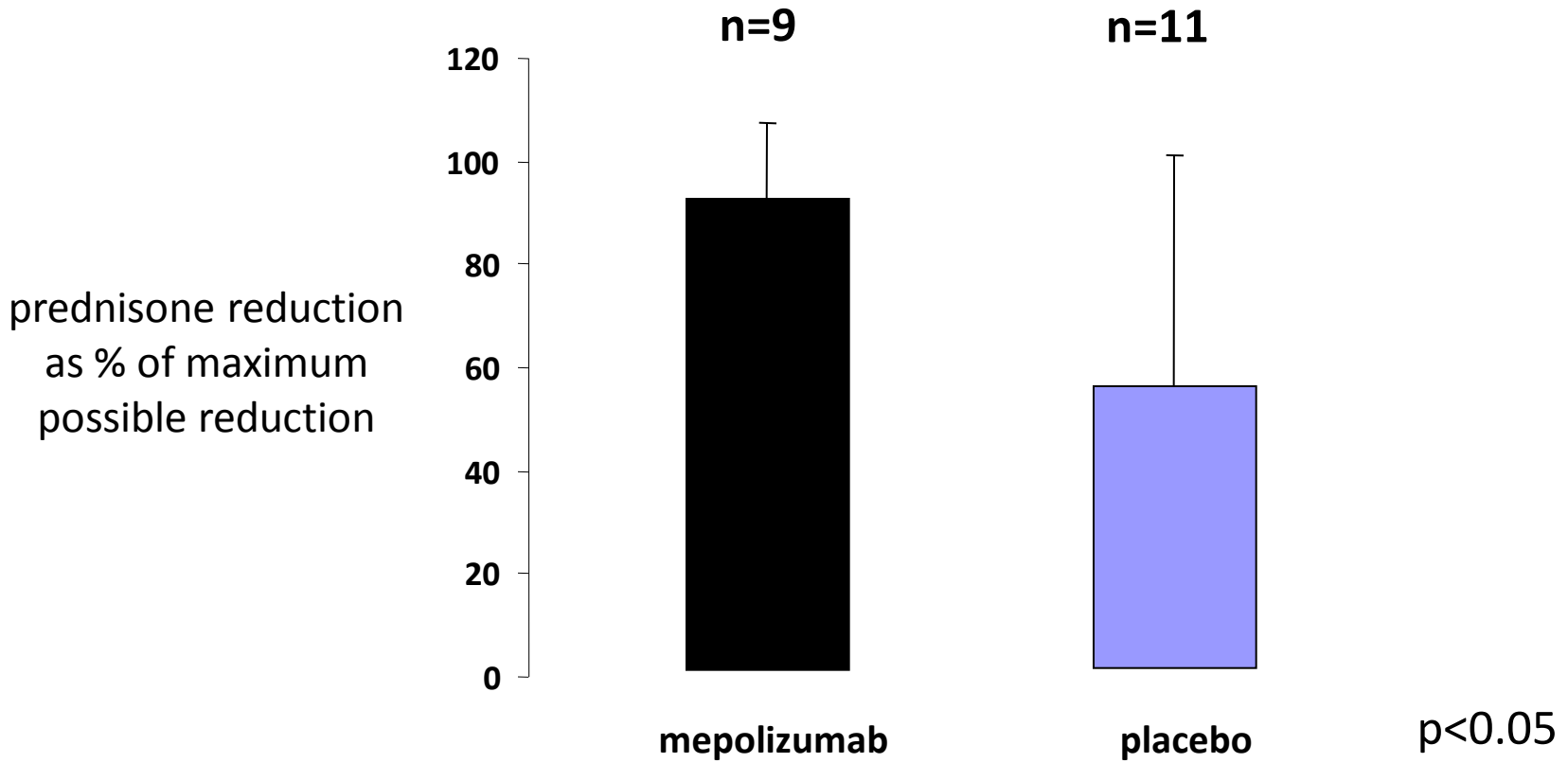
ORIGINAL ARTICLE

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

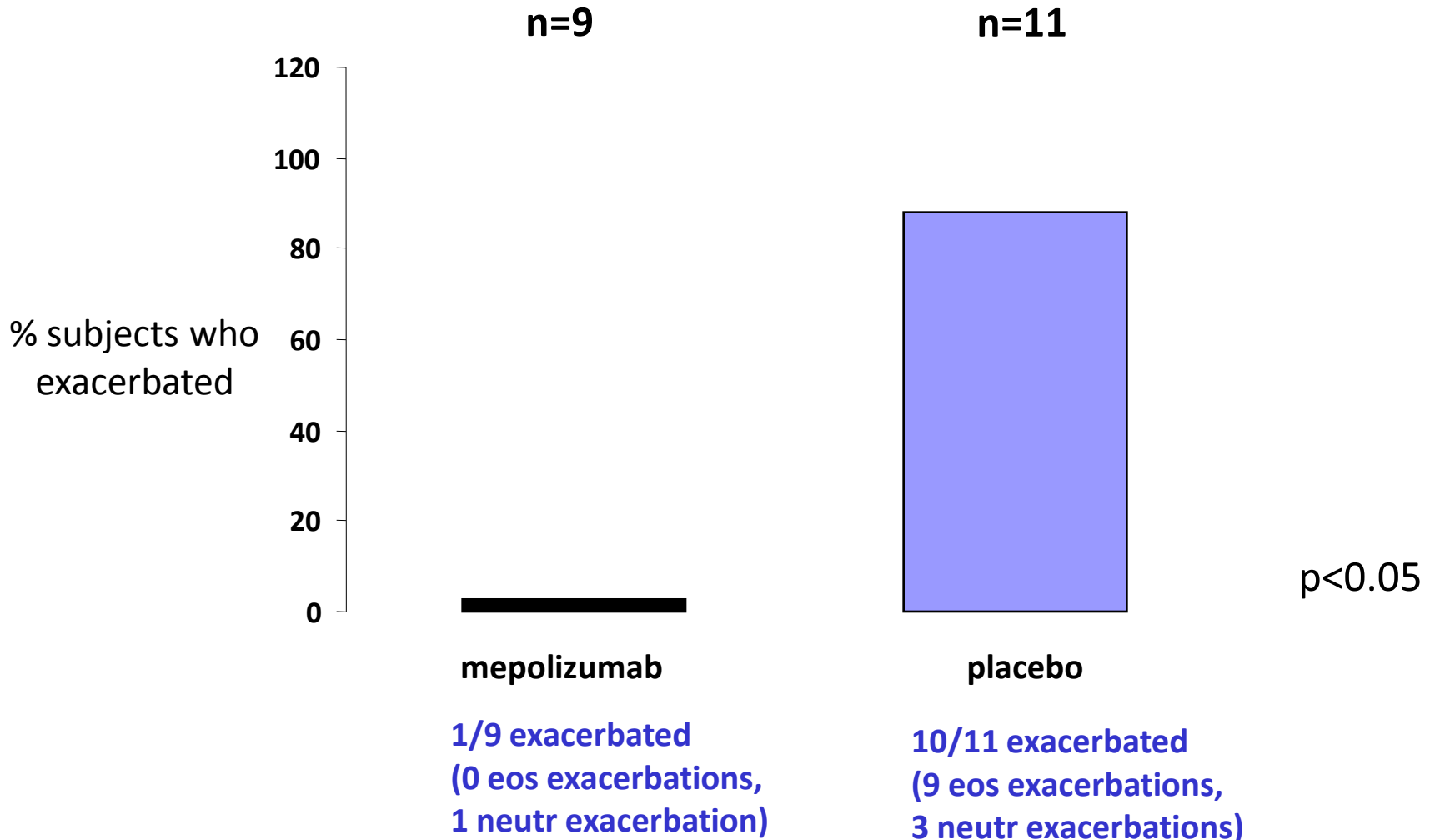
Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D.,
Melanie Kjarsgaard, R.R.T., Mark D. Inman, M.D., Ph.D.,
Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D.,
Frederick E. Hargreave, M.D., and Paul M. O'Byrne, M.B.

NEJM 2009; 360: 985-93

Primary Outcome



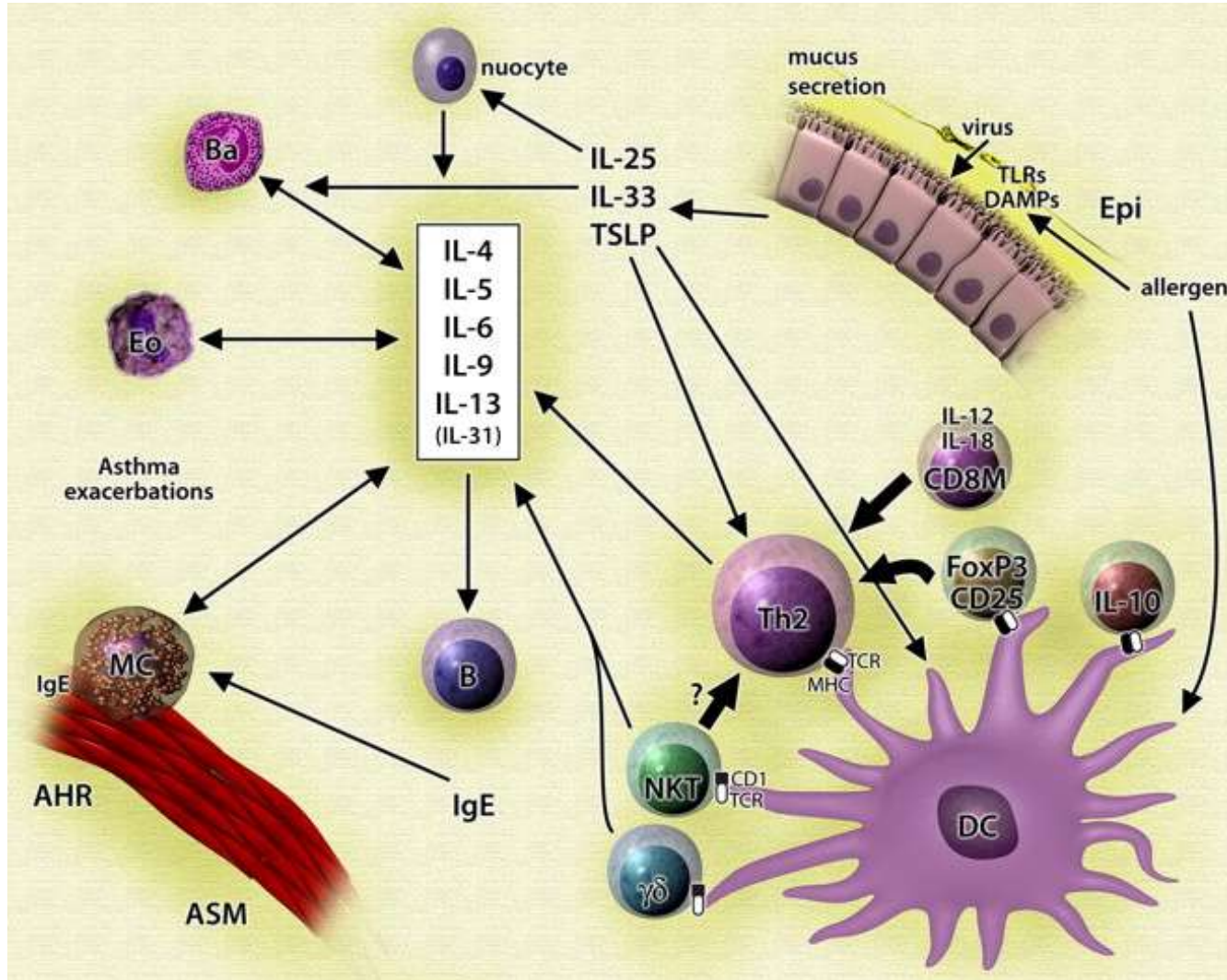
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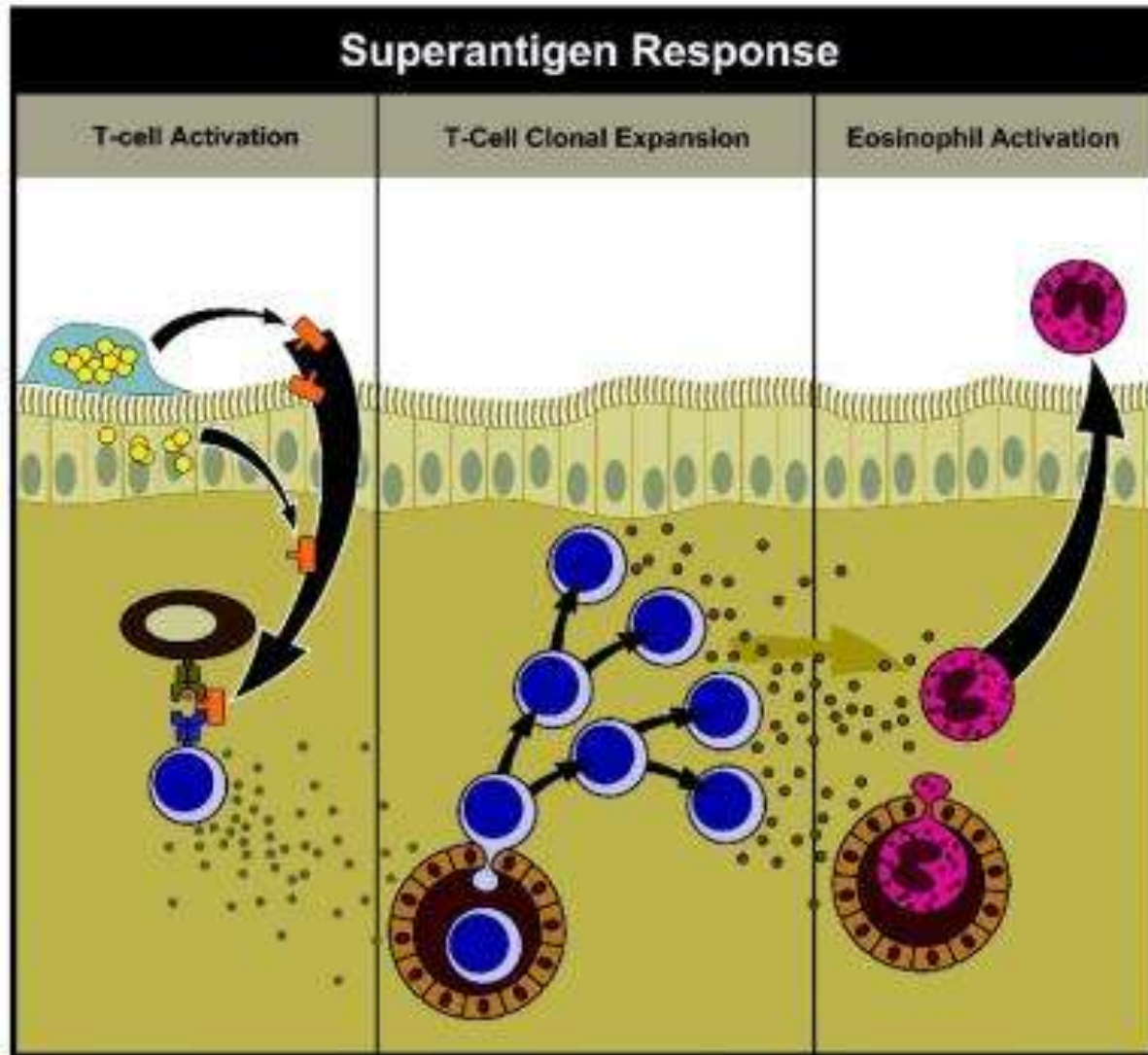
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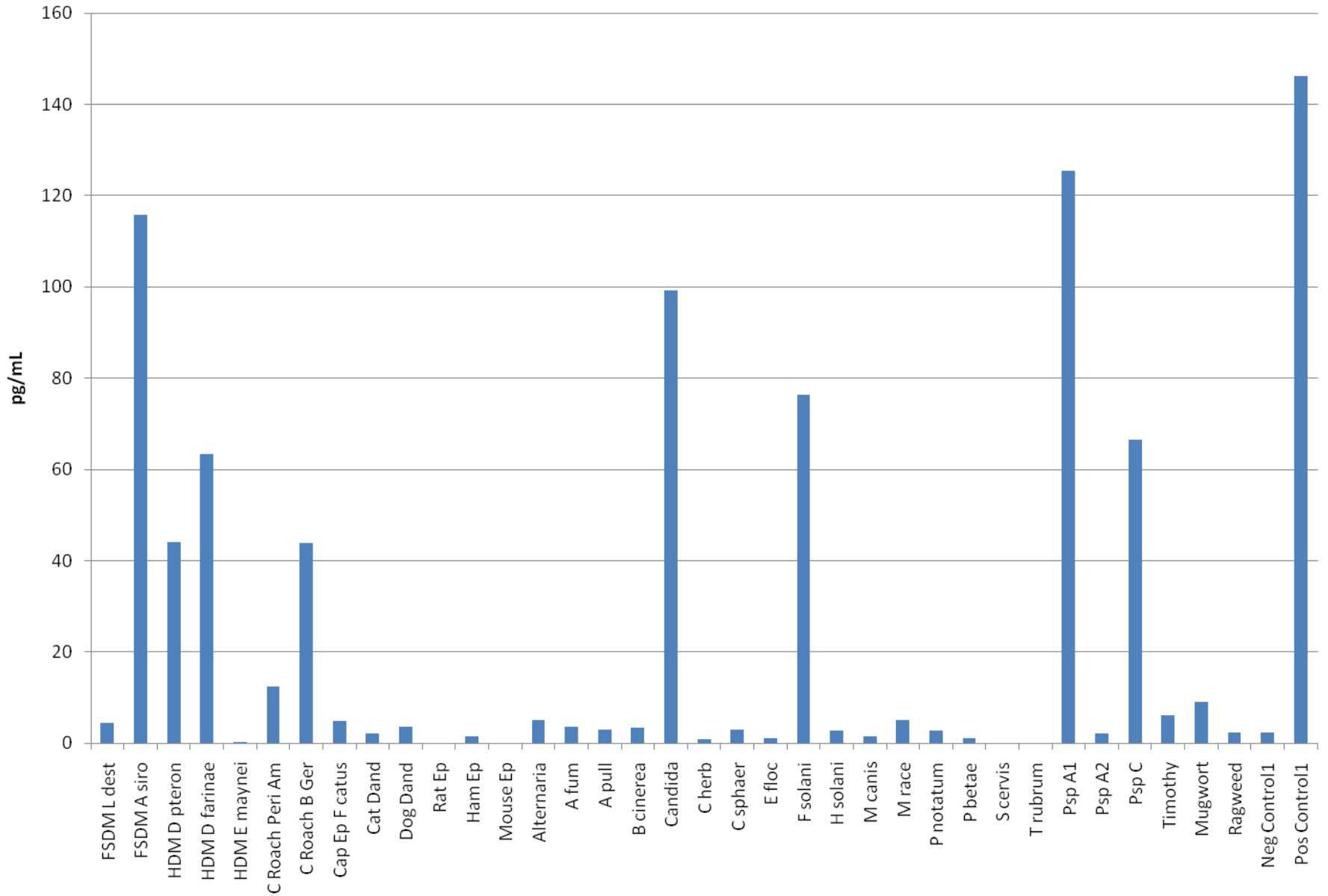
Non-IgE mediated inflammation T-cell



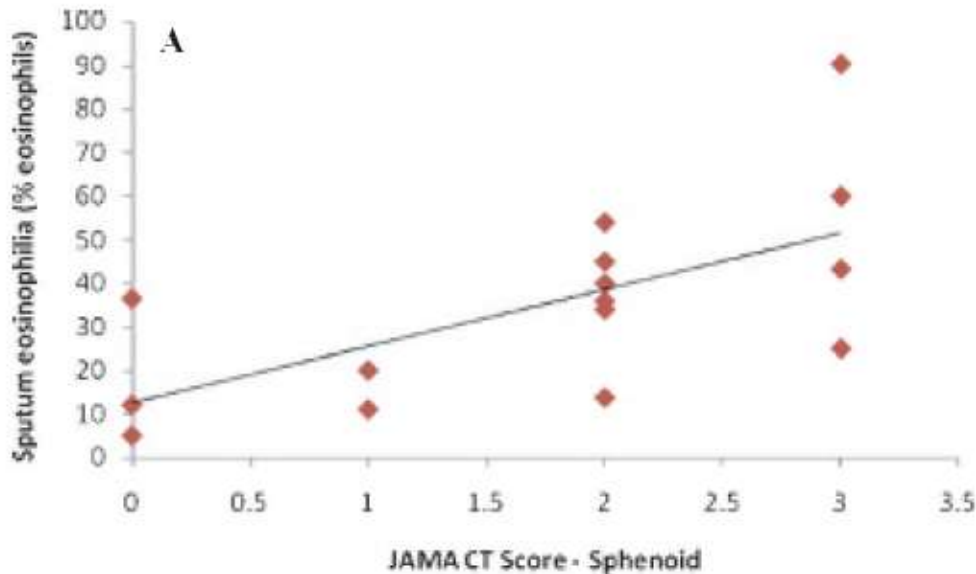
Sinusitis and T-cell activation



IL-5 from mononuclear cells



Is sinus surgery prednisone sparing?



- RCT
- Outcome: prednisone sparing
- Mechanisms
 - TSLP
 - SPINK
 - S100
 - IL5

Case history -4

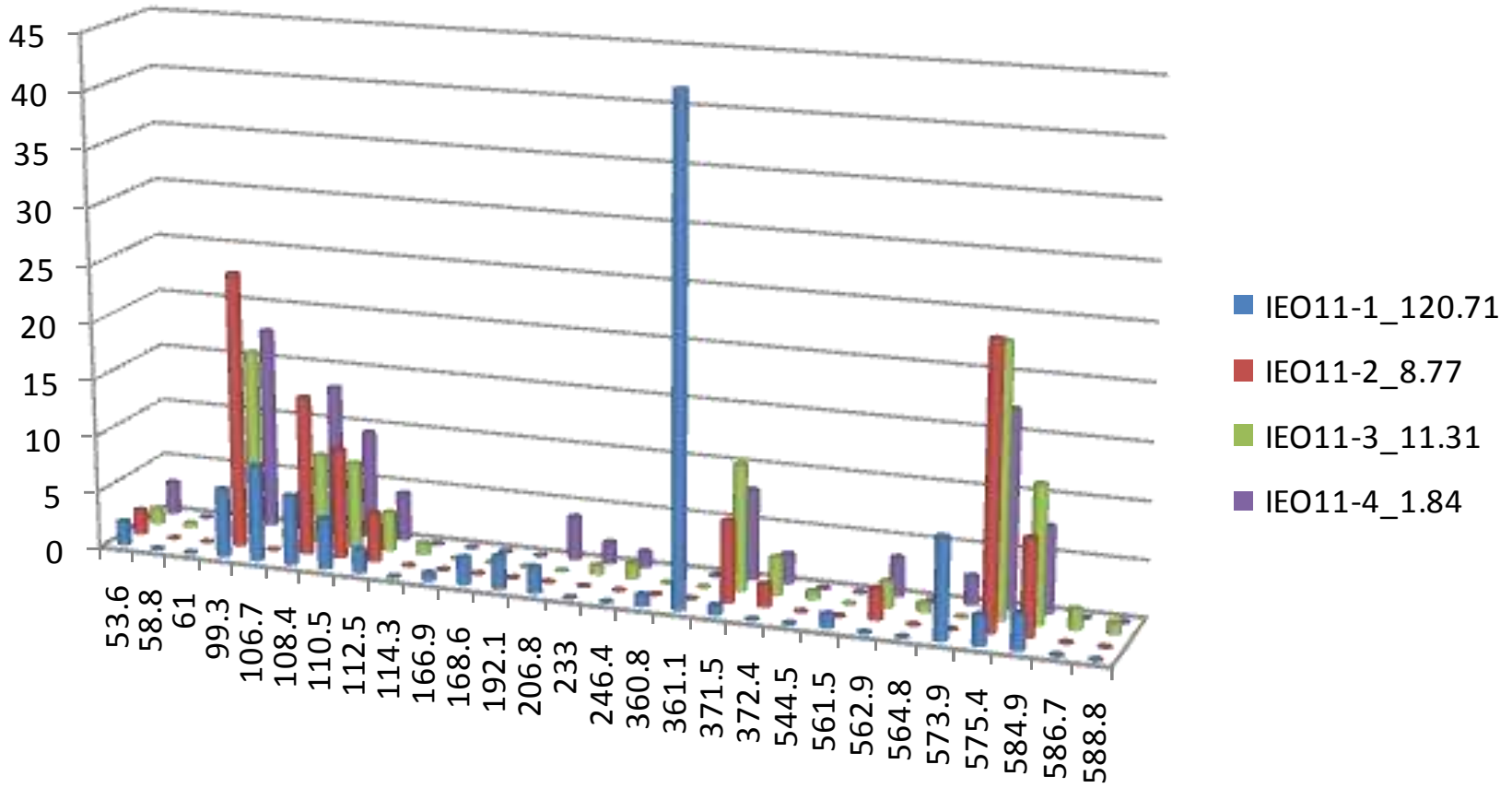
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Case history -4

Date	TCC	N	Eos
10/2/09	129	97	0.3
27/3/09	32	90	0
15/1/10	35	92	0
1/9/10	1.4	35.5	0

- Culture negative for bacteria, virus, mycobacteria
- PCR negative for Chlamydia
- Negative for CF mutations, normal sweat chloride
- Normal neutrophil function (chemotaxis, oxidative burst)
- Normal ciliary motility

Molecular diagnostics: t-RFLP



Airway microbiome by t-RFLP

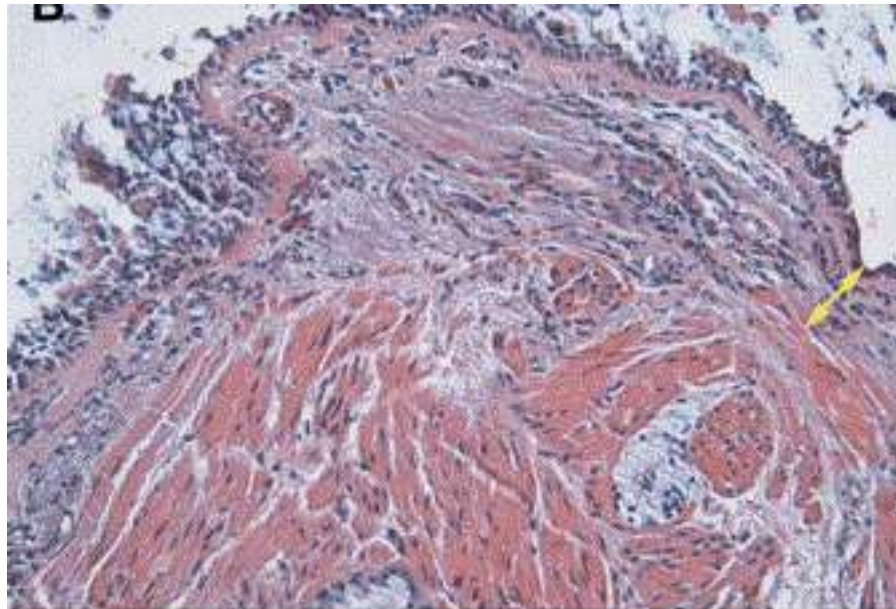
- Prevotella (96%)
- Veilonella (30%)
- Streptococcus milleri (91%)
- Actinomyces (49%)
- Granulicatella (46%)

Case history -5

- 45 female, 8-10 puffs of salbutamol daily
- Non-Atopic, never smoked
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- Fluticasone +salmeterol 500 bid, montelukast 10 mg, prednisone 5 mg, Cellcept 250 bid theophylline 200 mg

Case history -5

“ the airway appeared to some extent normal, but several areas of narrowing with stranding of smooth muscle appeared to be contracted and tethering the mucosa within the airway. The airways were extremely reactive to touch with the tip of the bronchoscope and this seemed excessive”



Treatment of hyperresponsiveness

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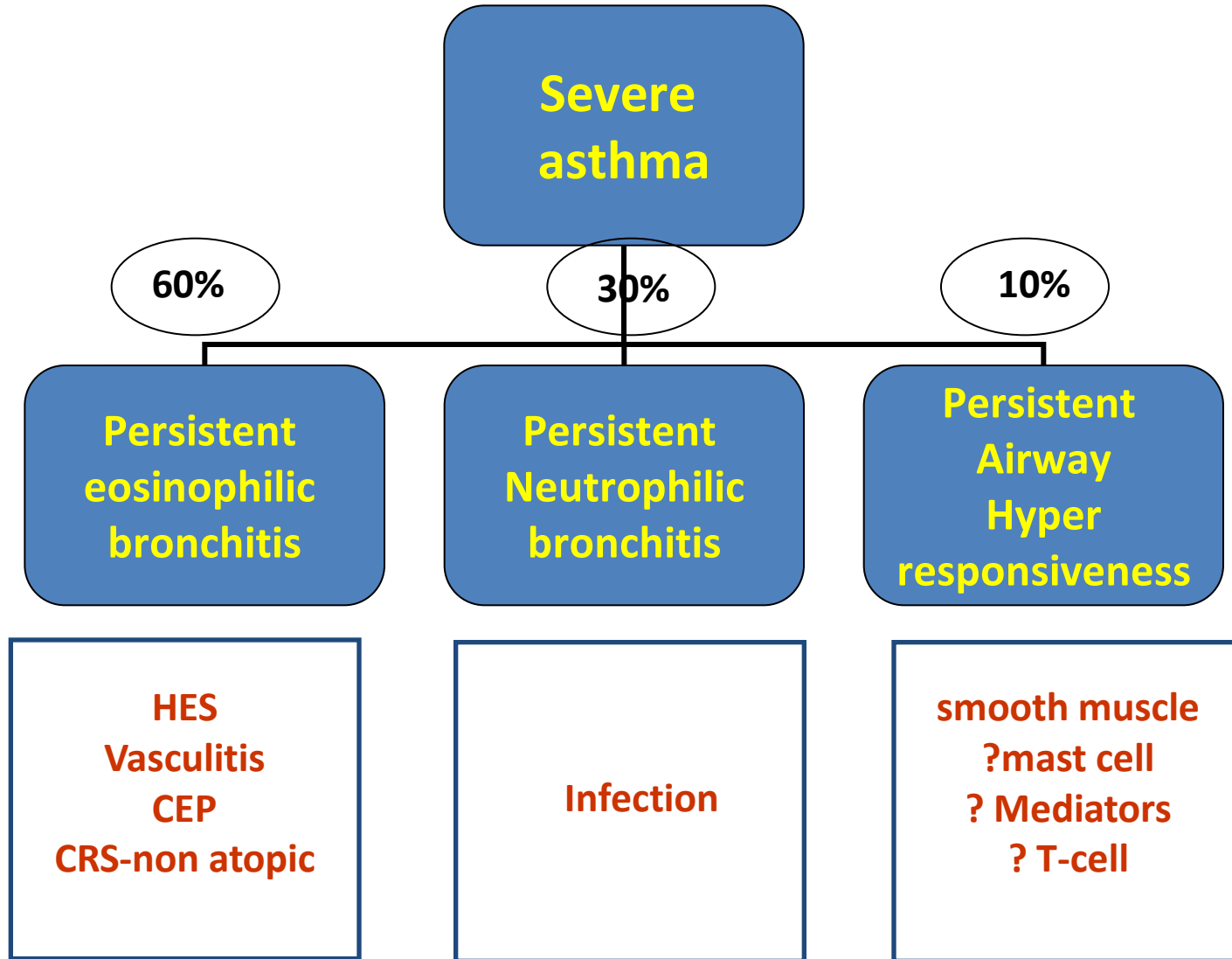
ORIGINAL ARTICLE

Asthma Control during the Year after Bronchial Thermoplasty

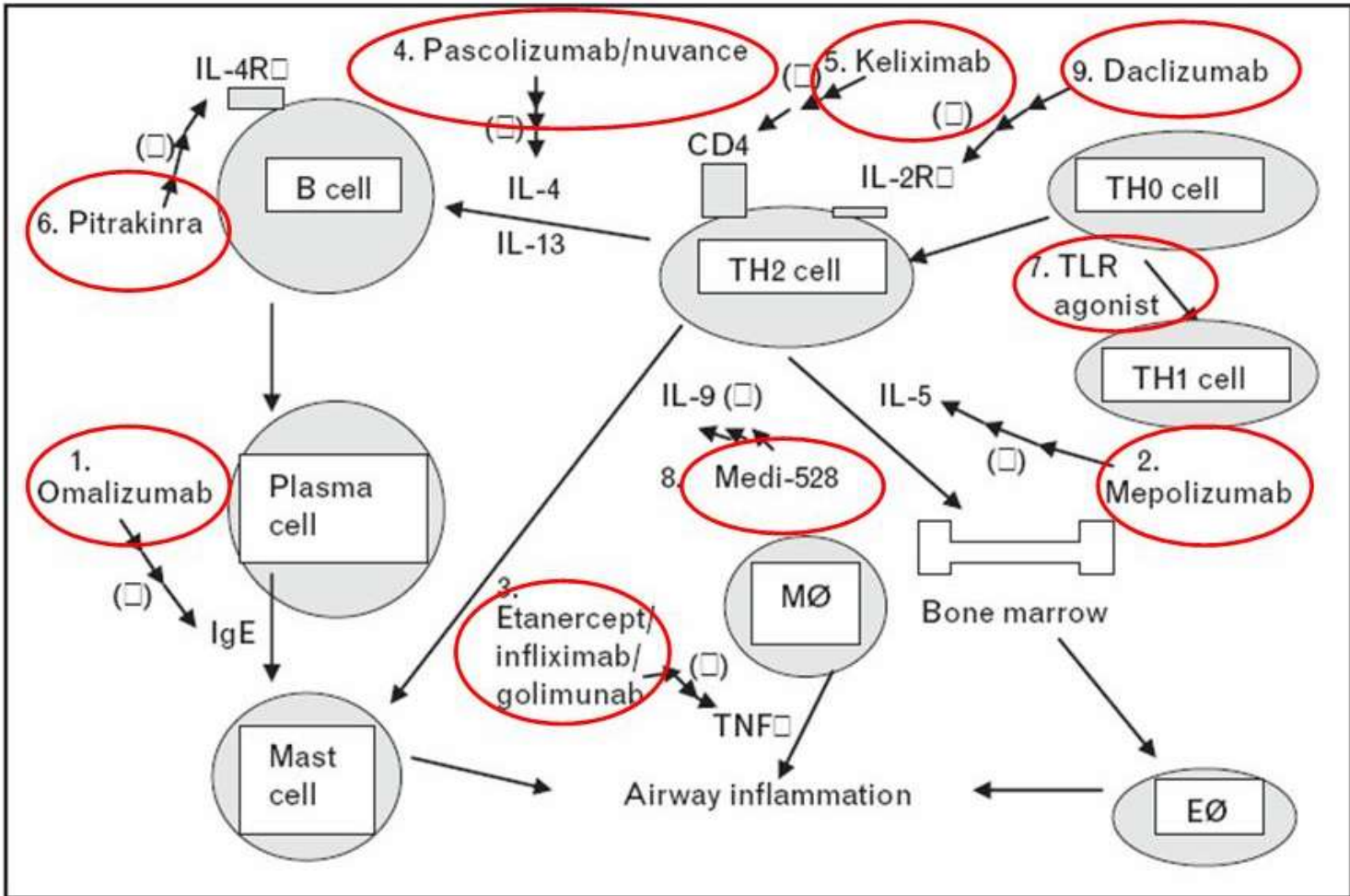
Gerard Cox, M.B., Neil C. Thomson, M.D., Adalberto S. Rubin, M.D.,
Robert M. Niven, M.D., Paul A. Corris, M.D., Hans Christian Siersted, M.D.,
Ronald Olivenstein, M.D., Ian D. Pavord, M.D., David McCormack, M.D.,
Rekha Chaudhuri, M.D., John D. Miller, M.D., and Michel Laviolette, M.D.,
for the AIR Trial Study Group*

Cox, NEJM 2007

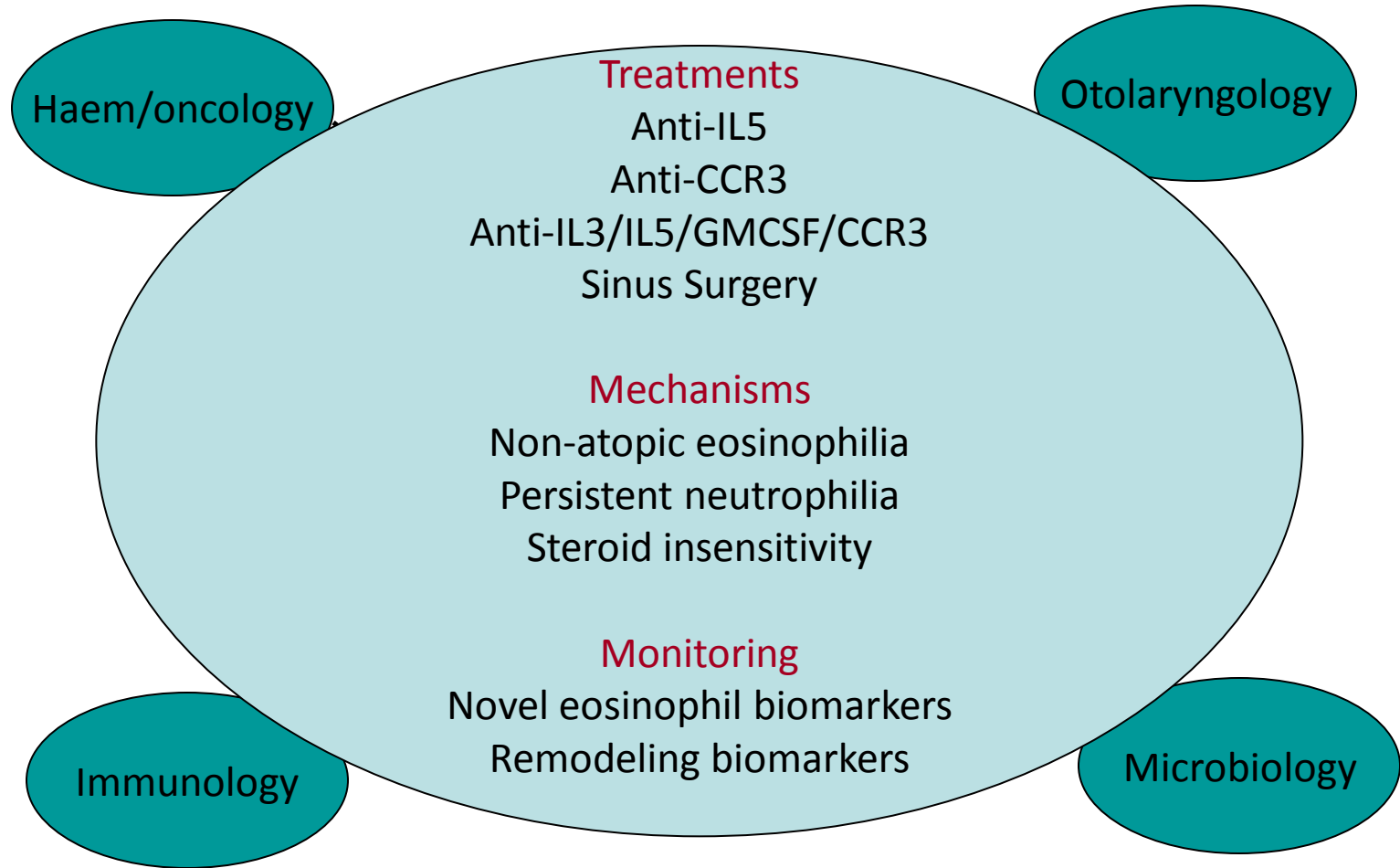
What contributes to asthma severity?



Biologics for asthma



A regional program



Our clinical experience

- 88 patients in severe asthma clinic
- Median age 40, females 52
- Current treatment
 - Prednisone, median daily dose 10 mg (4-45)
 - Mepolizumab 2
 - IV IG 4
 - Nebulised saline 6
 - Long term antibiotics 5
 - Imatinib 2
 - Hydroxyurea 2
 - Methotrexate 1
- 14 have associated peripheral blood eosinophilia
 - HES: 4, ANCA –ve vasculitis: 2

The gains

- 0.2 eosinophilic exacerbations/year
- 0.5 neutrophilic exacerbations/year
- Loss of FEV1 35 ml/year
- Prednisone dose
 - increased in 65%
 - decreased in 25%
 - unchanged in 10%

The price

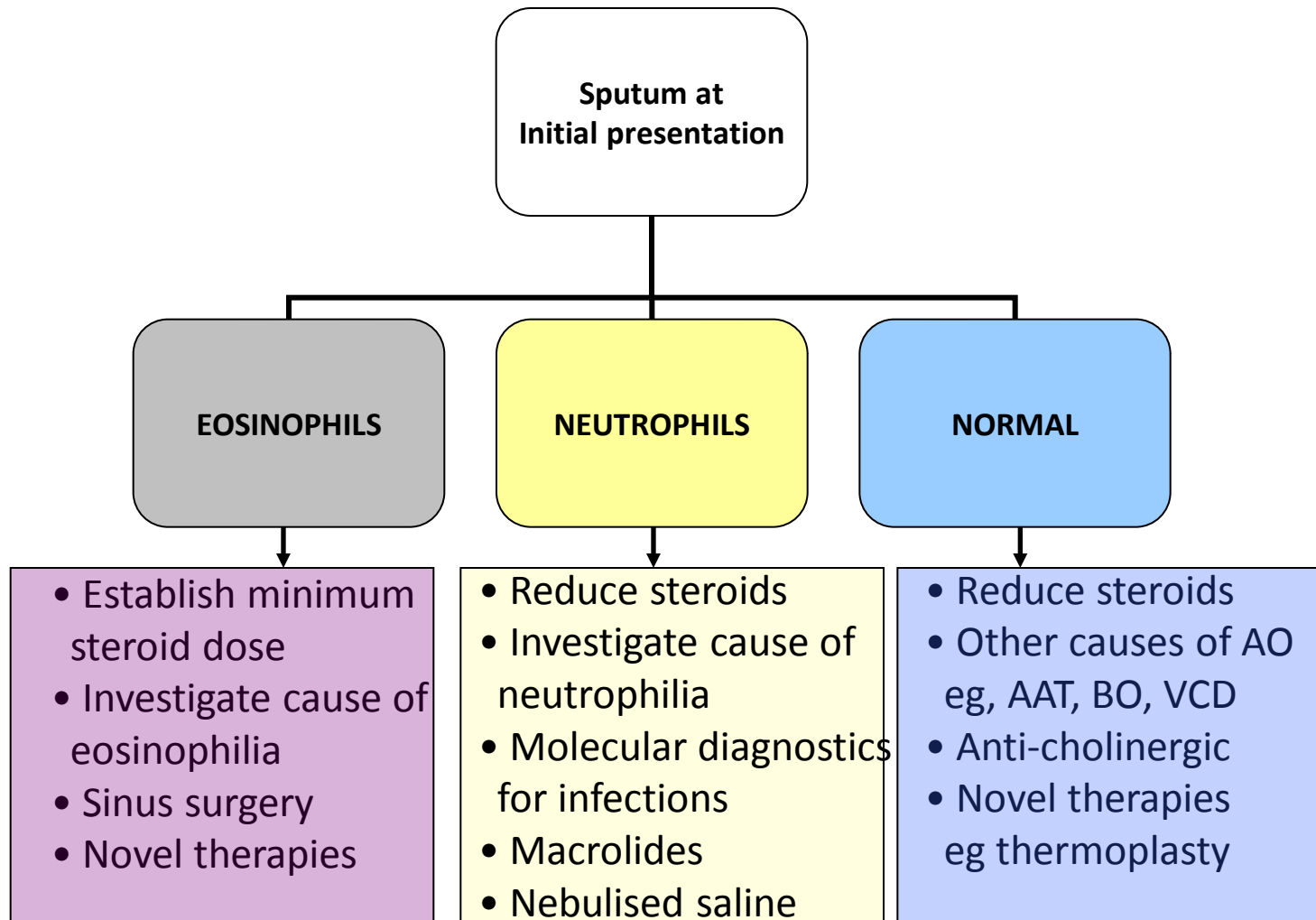
- Adverse effects of treatment

Osteoporosis/osteopenia	72%
Hypertension	60%
Recurrent bronchitis	58%
Cataract	42%
Skin bruising	35%
Diabetes	16%
Glaucoma	14%

- Shrinking resources

- Strain on the research lab

Summary



Putting it in perspective

RRR of rate of exacerbation in ASTHMA studies

FACET NEJM 1997	50%
GOAL AJRCCM 2004	10-15%
TALC NEJM 2010	~5%
OMALIZUMAB ANN INTERN MED 2011	25%
MONTELUKAST BMJ 2003	~3%
THERMOPLASTY AJRCCM 2008	32%
SPUTUM STRATEGY ERJ 206	49%