ΕΝΤΕΡΟΤΟΞΙΝΕΣ ΚΑΙ ΣΟΒΑΡΟ ΑΣΘΜΑ

ΣΧΟΙΝΗ ΠΗΝΕΛΟΠΗ
ΕΙΔΙΚΕΥΟΜΕΝΗ ΠΝΕΥΜΟΝΟΛΟΓΙΑΣ-ΦΥΜΑΤΙΟΛΟΓΙΑΣ
4Η ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ, ΝΝΘΑ «Η ΣΩΤΗΡΙΑ»

ΣΟΒΑΡΟ ΑΣΘΜΑ

Άσθμα που απαιτεί θεραπεία σταδίων 4 και 5 κατά GINA (υψηλές δόσεις ICS και LABA ή τροποποιητές λευκοτριενίων /θεοφυλλίνη) για τον προηγούμενο χρόνο ή συστηματικά στεροειδή για >50% του προηγούμενου χρόνου προκειμένου να μη γίνει μη ελεγχόμενο ή το οποίο παραμένει μη ελεγχόμενο παρά τη θεραπεία

Ως μη ελεγχόμενο άσθμα ορίζεται ως τουλάχιστον ένα από τα παρακάτω:

1. Πτωχός έλεγχος συμπτωμάτων: με ACQ μονίμως >1,5 ή ACT <20
2. Συχνές σοβαρές παροξύνσεις : 2 ή περισσότερες με ανάγκη για συστηματικά στεροειδή πάνω από 3 ημέρες τον προηγούμενο χρόνο
3. Σοβαρές παροξύνσεις : με τουλάχιστον μία νοσηλεία, παραμονή σε ΜΕΘ ή μηχανικό αερισμό τον προηγούμενο χρόνο
4. Περιορισμός ροής παρά τη σωστή βρογχοδιαστολή με FEV1 <80% του προβλεπόμενου (με FEV1/FVC κατώτερου του κατώτερου φυσιολογικού ορίου

Ελεγχόμενο άσθμα που επιδεινώνεται επί σταδιακής μείωσης εισπνεόμενων ή συστηματικών στεροειδών.

ERS/ATS GUIDELINES ON SEVERE ASTHMA

ΕΝΤΕΡΟΤΟΞΙΝΕΣ

Staphylococcus aureus:

- ευκαιριακό παθογόνο του δέρματος και των βλεννογόνων

Παράγει:

- Θερμοανθεκτικές υψηλού μοριακού βάρους διαλυτές πρωτεΐνες
- Τρεις μεγάλες κατηγορίες A (SEA), B (SEB) , I (συνολικά 20 !!)
- Γνωστή η συσχέτισή τους με ρινικούς πολύποδες και αλλεργική ρινίτιδα
- Δράση ως υπεραντιγόνα

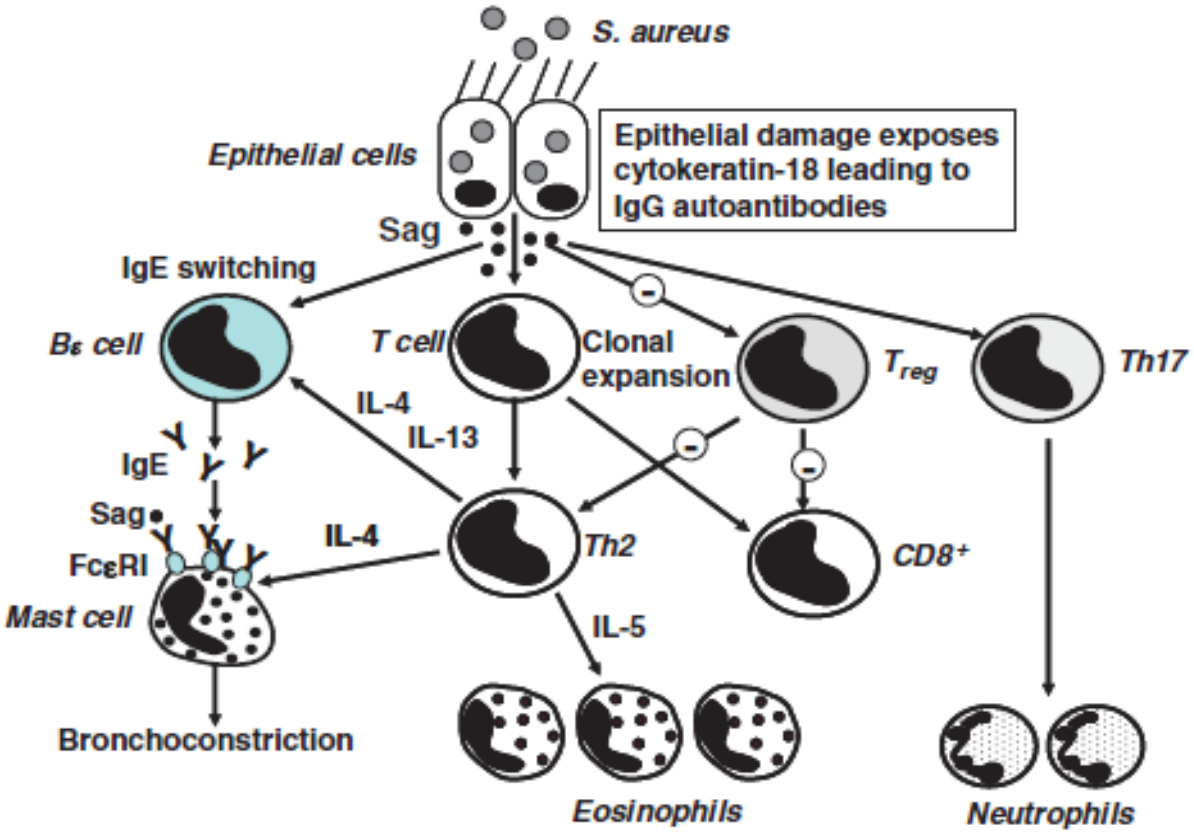

Fig. 1. Possible microbial mechanism of intrinsic asthma. Invasion of airway epithelial cells by *Staphylococcus aureus* (and other microorganisms) causes the release of Staphylococcal superantigens (Sag) (and other superantigens), which act on airway B lymphocytes to cause class-switching with the local production of polyclonal IgE, together with IgE directed against SSa (which acts as a 'superallergen'). This causes mast cell activation and release of bronchoconstrictor mediators and sensitizes mast cells to activation by triggers, such as exercise and cold air (via changes in surface osmolality). SSa also cause polyclonal expansion of T cells, resulting in increased T-helper type 2 (Th2) cells and $CD8^+$ cells. Th2 cells release IL-9, which induces the expression of high-affinity IgE receptors (FcεRI) in mast cells and IgE synthesis by B cells (together with IL-13). IL-5 promotes eosinophilic inflammation. SSa may also reduce corticosteroid responsiveness in T cells, resulting in the need for higher doses to control asthma. SSa also inhibit the function of regulatory T cells (Treg), resulting in further enhancement of Th2 and $CD8^+$ cells. SSa may also activate Th17 cells, leading to neutrophilic inflammation. Staphylococcal infection of epithelial cells may also lead to damage and exposure of epitopes on epithelial structural proteins, such as cytokeratin-18, resulting in the formation of cytotoxic IgG antibodies, which further damage epithelial cells, making them more susceptible to further microbial colonization.

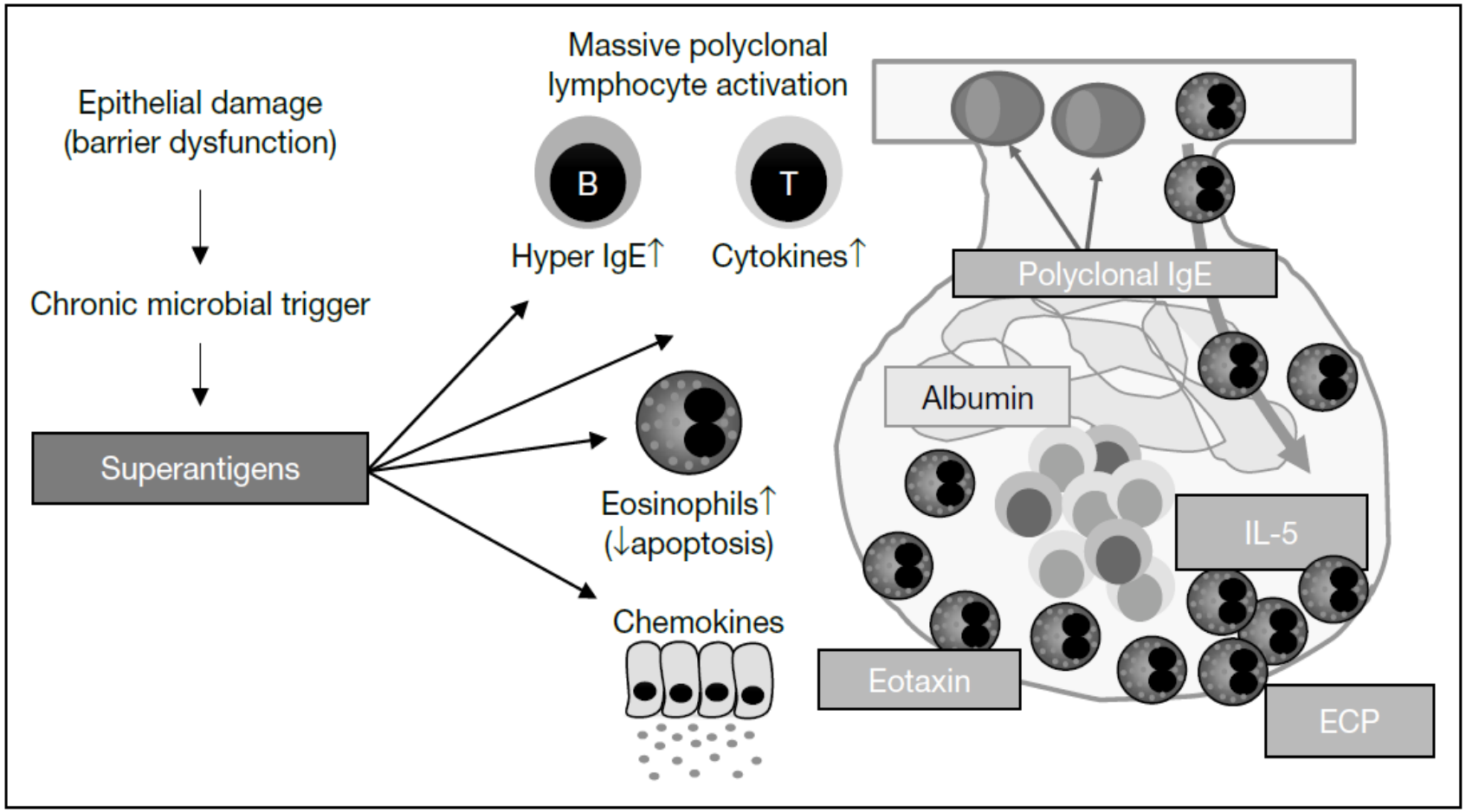

Fig. 1. The superantigen hypothesis: Superantigens, once passed the epithelial barriere, induce polyclonal T-cell and B-cell activiation and a Th2-biased eosinophilic inflammation in the airways.

Role of Staphylococcal Superantigens in Airway Disease

C. Bachert, P. Gevaert, Nan Zhang, T. van Zele, Claudina Perez-Novo

Upper Airway Research Laboratory, ENT Department, University Hospital Ghent, Ghent, BelgiumMarone G (ed): Superantigens and Superallergens. Chem Immunol Allergy. Basel, Karger, 2007, vol 93, pp 214–23

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AAIR
Allergy, Asthma & Immunology Research

IL-5 Promoter Polymorphism Enhances IgE Responses to Staphylococcal Superantigens in Adult Asthmatics

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Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea

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Annals of Allergy, Asthma & Immunology

Staphylococcus aureus enterotoxin sensitization involvement and its association with the *CysLTR1* variant in different asthma phenotypes

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SEA /SEB ΚΑΙ ΠΙΘΑΝΟΤΗΤΑ ΕΜΦΑΝΙΣΗΣ ΑΣΘΜΑΤΟΣ

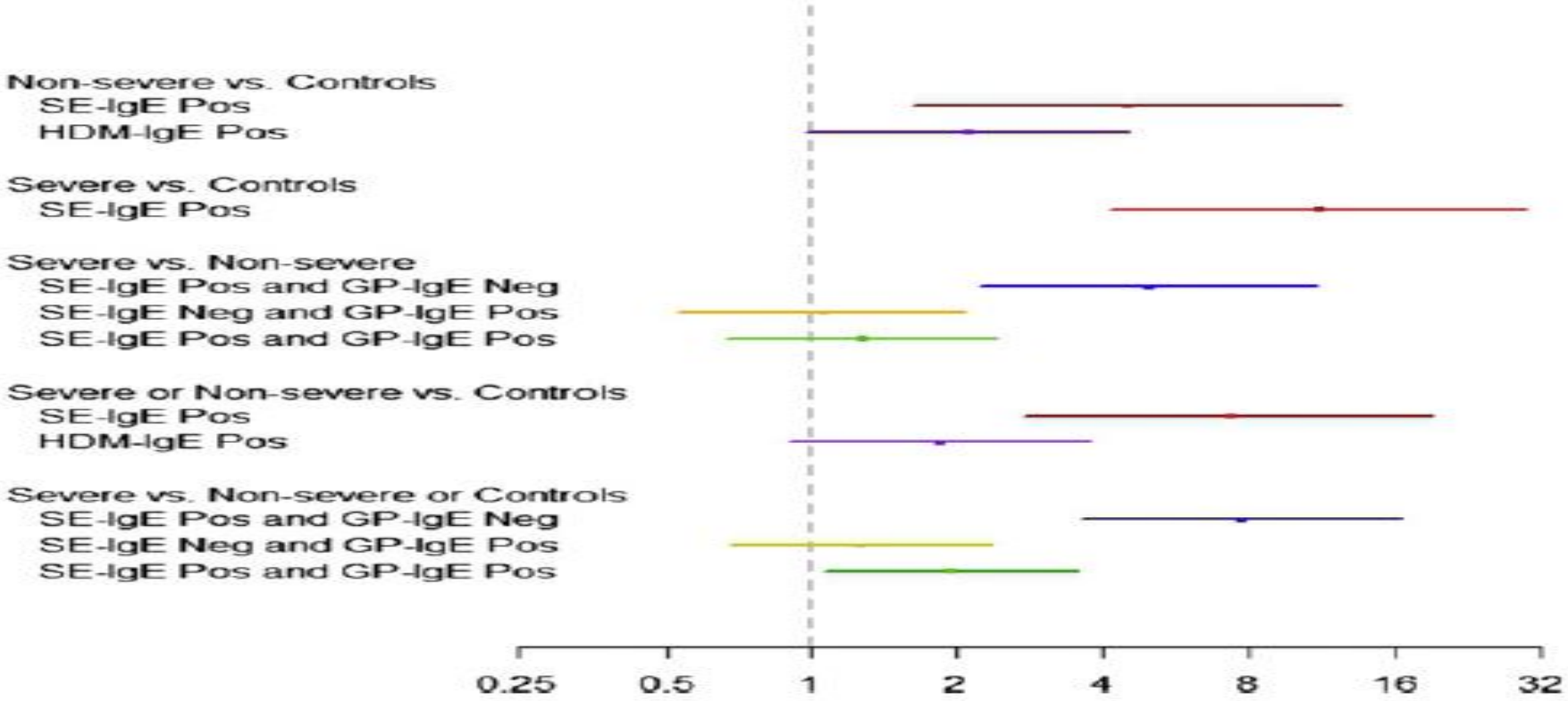

FIG 1. Logistic regression models for disease severity. ORs and 95% CIs are represented for the different comparisons. SE IgE levels in serum were associated with a significantly increased risk of asthma (OR, 7.26; 95% CI, 2.76-19.13; $P < .001$) and especially severe asthma (OR, 11.09; 95% CI, 4.14-29.68; $P < .001$).

Specific IgE against Staphylococcus aureus enterotoxins: An independent risk factor for asthma
Claus Bachert, MD, PhD, et al. J ALLERGY CLIN IMMUNOL AUGUST 2012

Ο ΡΟΛΟΣ ΤΩΝ SEA /SEB ΣΕ ΒΡΟΓΧΙΚΟ ΑΣΘΜΑ ΚΑΙ ΑΛΛΕΡΓΙΚΗ ΡΙΝΙΤΙΔΑ

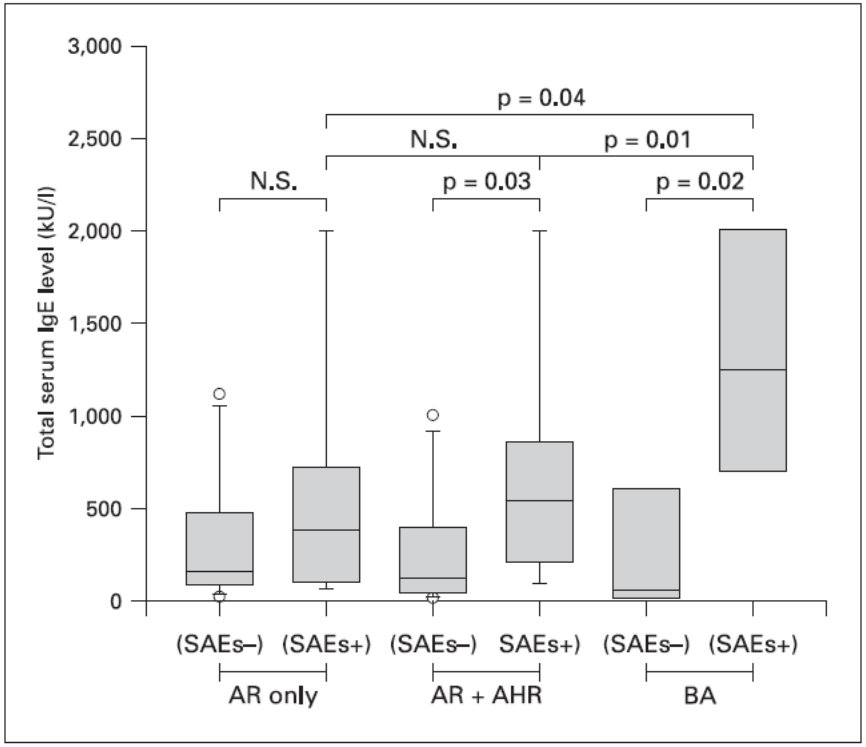

Fig. 1. Comparison of total serum IgE levels between subgroups of the AR/BA only group with (SAEs+) or without (SAEs–) sensitization to SEA/SEB. The boundary of the box indicates the 25th–75th percentile of the total serum IgE level, the line marks the median. N.S. = Not significant.

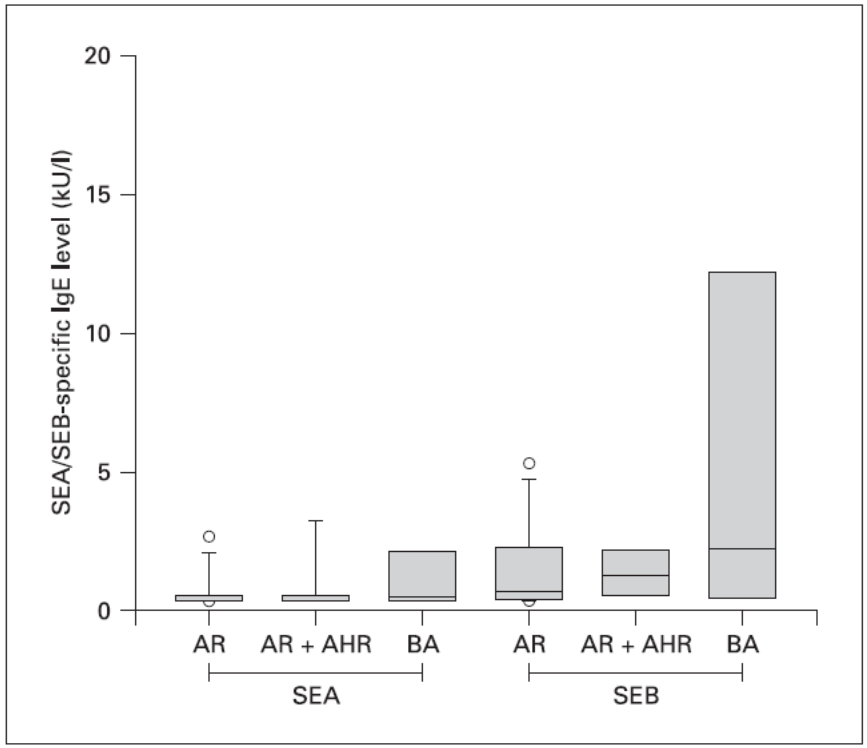

Fig. 2. Comparison of SEA- and SEB-specific IgE levels between subgroups of the AR/BA only group. The boundary of the box indicates the 25th–75th percentile of the SEA/SEB-specific IgE level, the line marks the median.

Increased Levels of Serum-Specifi c Immunoglobulin E to Staphylococcal Enterotoxin A and B in Patients with Allergic Rhinitis and Bronchial Asthma
Jyh-Hong Lee et al. Int Arch Allergy Immunol 2005;138:305–311

Ο ΡΟΛΟΣ ΤΩΝ SEA ΚΑΙ SEB ΣΤΟΥΣ ΕΦΗΒΟΥΣ ΚΑΙ Η ΕΠΙΡΡΕΠΕΙΑ ΣΤΟ ΑΣΘΜΑ

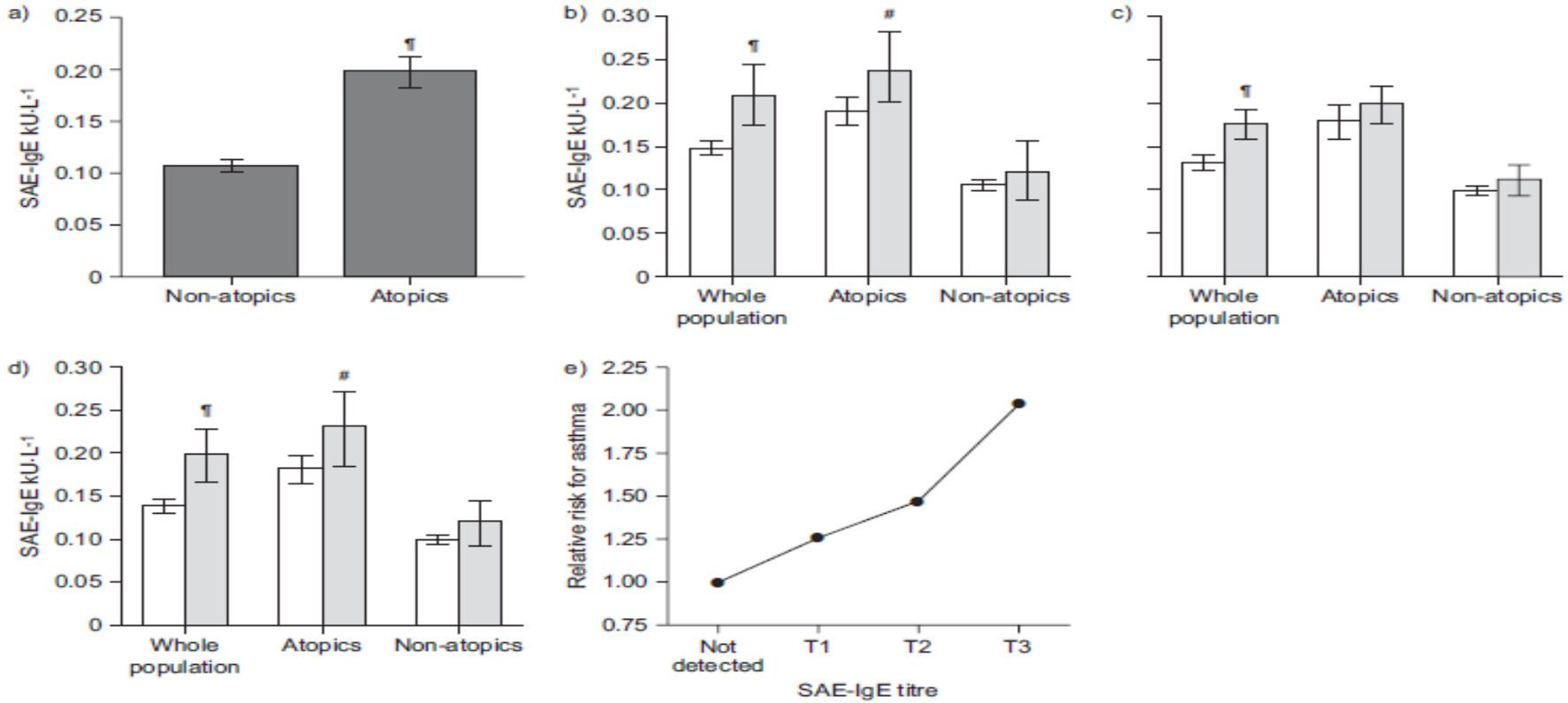

FIGURE 1. *Staphylococcus aureus* enterotoxin (SAE)-immunoglobulin (Ig)E titres within subgroups of the cohort. a) Data shown are geometric means (95% CI) of SAE-IgE titres stratified by atopy. b, c, d) Data shown are geometric means (95% CI) of SAE-IgE titres stratified by clinical outcomes in b) asthma, c) rhinoconjunctivitis and d) bronchial hyperresponsiveness in the whole population and atopic and non-atopic subgroups. □: disease not present; ■: disease present. e) Subjects with detectable SAE-IgE titres were split into terciles according to SAE-IgE: T1: 0.15–0.23 kU·L^{-1}; T2: 0.24–0.50 kU·L^{-1}; T3: 0.51–30.9 kU·L^{-1}. Risk of asthma was computed from univariate logistic regression and presented as mean risk of asthma amongst subjects in each tercile relative to subjects with undetectable SAE-IgE titres. p=0.000. Comparisons between groups (a–d) were assessed by Mann–Whitney U-test. #: $p \leq 0.05$; ¶: $p \leq 0.005$.

Th2-associated immunity to bacteria in teenagers and susceptibility to asthmaE.M. Hollams*, B.J. Hales*, C. Bachert#, W. Huvenne#, F. Parsons*, N.H. de Klerk*, M. Serralha*, B.J. Holt*, S. Ahlstedt", W.R. Thomas*, P.D. Sly* and P.G. Holt*Eur Respir J 2010; 36: 509–516DOI: 10.1183/09031936.00184109CopyrightERS 2010

SEA /SEB ΣΕ ΑΣΘΕΝΕΙΣ 20 ΕΤΩΝ ΜΕ ΑΣΘΜΑ

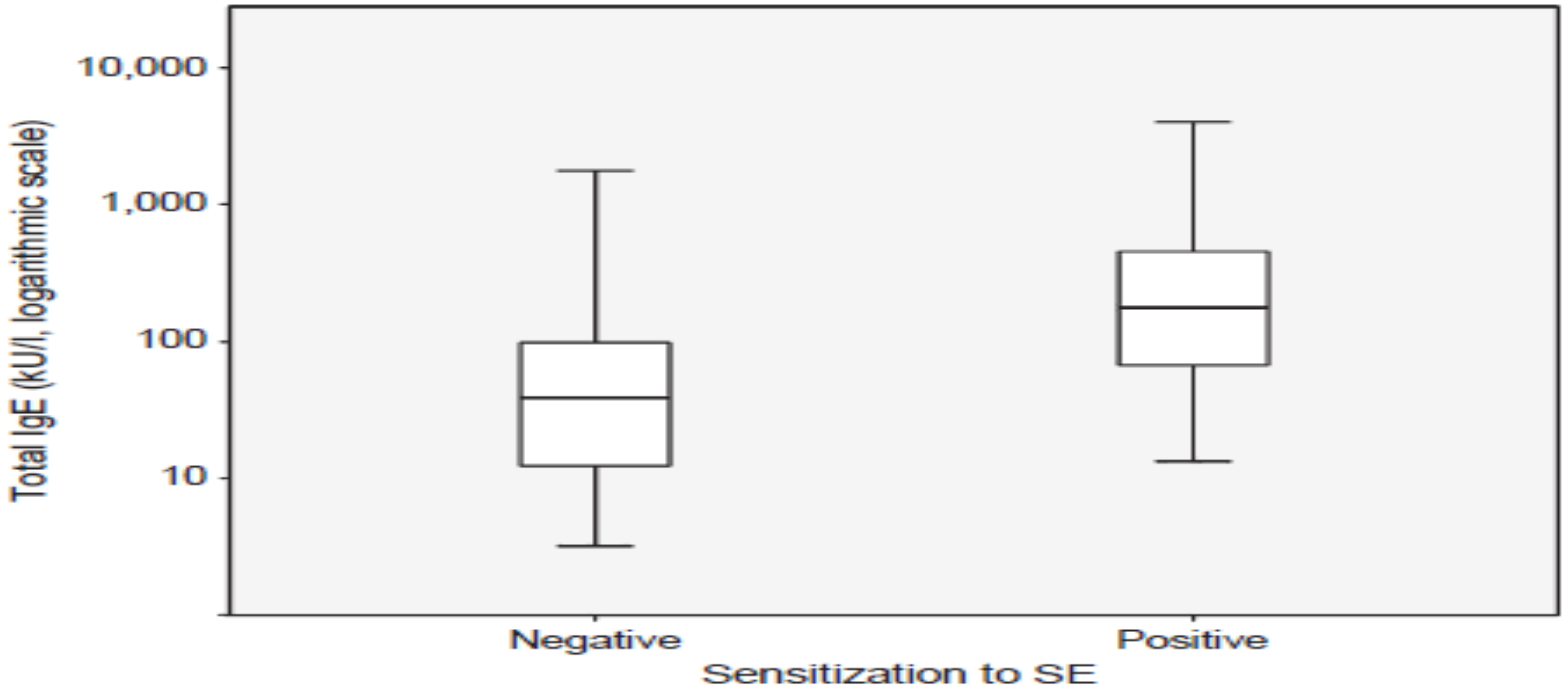

Figure 1 Concentration of total IgE according to sensitization to SE. The total IgE level is significantly higher in SE-IgE negative subjects compared to SE-IgE positive subjects ($p < 0.001$).

Is immunoglobulin E to Staphylococcus aureus enterotoxins associated with asthma at 20 years?
Ina Sintobin1, Thomas Keil2,3, Susanne Lau4, Linus Grabenhenrich2, Gabriele Holtappels1, Andreas Reich2, Ulrich Wahn4 & Claus Bachert1,5Pediatric Allergy and Immunology

Ο ΡΟΛΟΣ ΤΩΝ ΕΝΤΕΡΟΤΟΞΙΝΩΝ ΣΤΟ ΑΣΘΜΑ ΤΩΝ ΕΝΗΛΙΚΩΝ

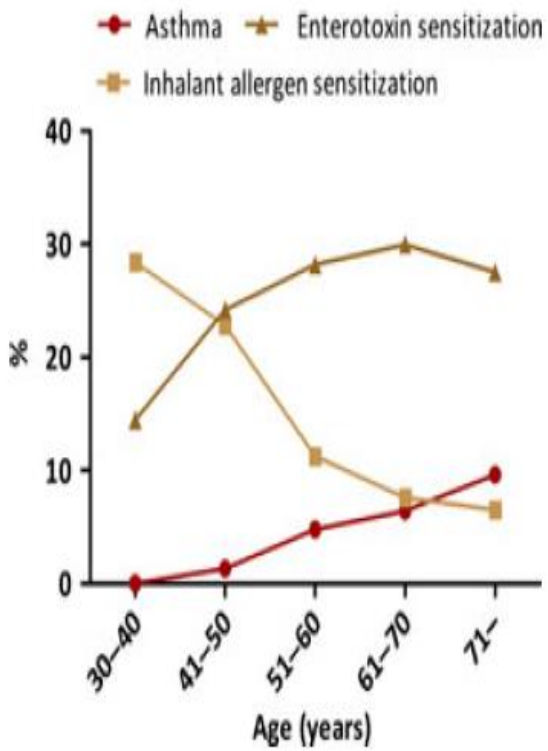

Fig. 1. Prevalence of current asthma, inhalant allergen sensitization and staphylococcal enterotoxin sensitization by age groups.

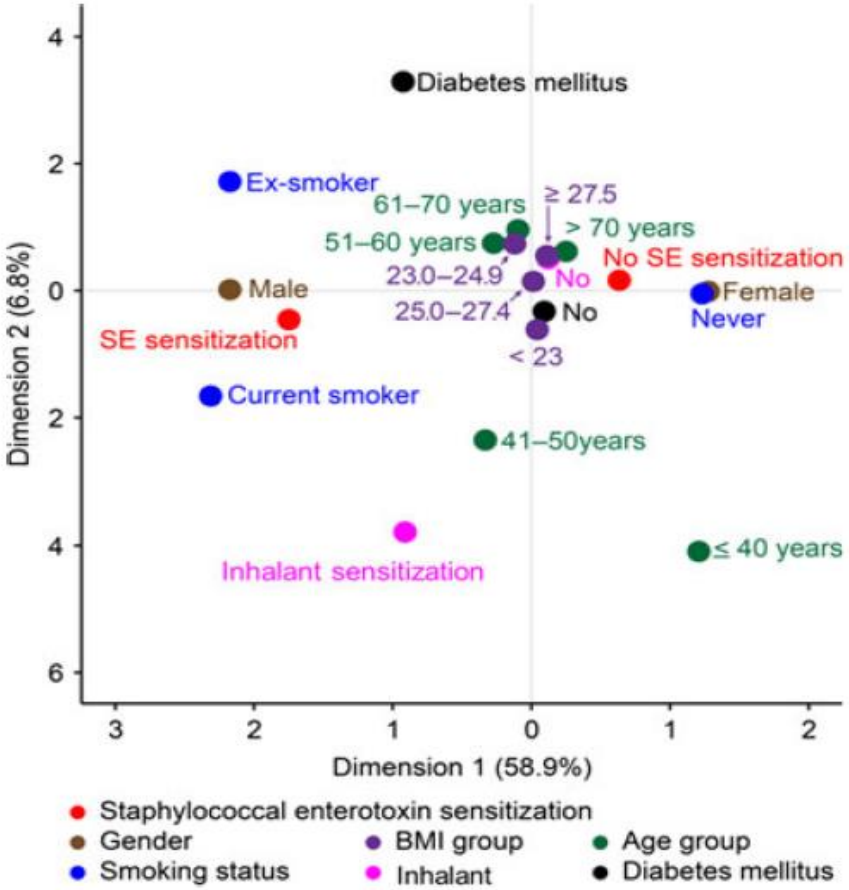

Fig. 2. Multiple correspondence analysis map representing the relationships between staphylococcal enterotoxin sensitization and six relevant factors that were identified in multivariate logistic regression tests

Staphylococcal enterotoxin sensitization in a community-based
population: a potential role in adult-onset asthma
W.-J. Song et al. Clinical & Experimental Allergy, 44, 553–562

SEA/SEB ΚΑΙ ΑΣΘΜΑ ΗΛΙΚΙΩΜΕΝΩΝ

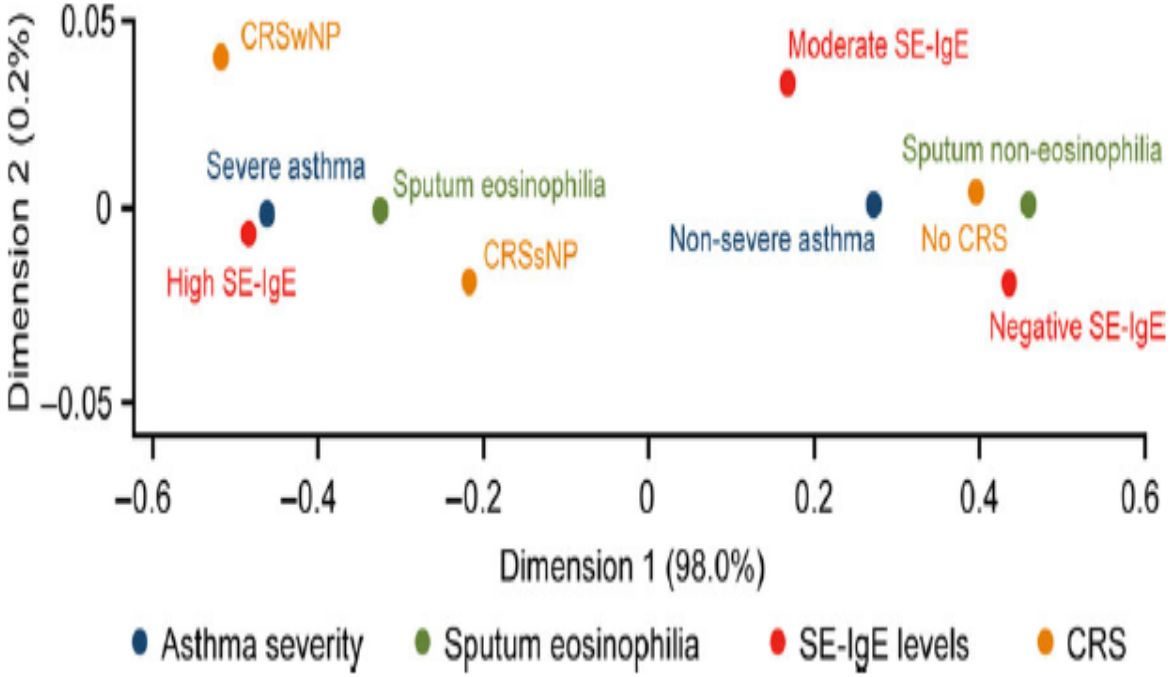

Fig. 1. Multiple correspondence analyses plot for the inter-relationships between severe asthma, CRS, sputum eosinophilia and serum SE-IgE levels among 186 elderly patients with asthma. Severe asthma is situated close to high SE-IgE (≥ 0.35 kU/L), CRSwNP and sputum eosinophilia (≥ 3%). CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; SE-IgE, staphylococcal enterotoxin-specific IgE.

Staphylococcal enterotoxin IgE sensitization in late-onset severe eosinophilic asthma in the elderly
W.-J. Song et al. Clinical & Experimental Allergy, 46, 411–421

SEA/SEB ΚΑΙ ΑΣΘΜΑ ΜΕ ΚΑΠΝΙΣΤΙΚΟ ΙΣΤΟΡΙΚΟ

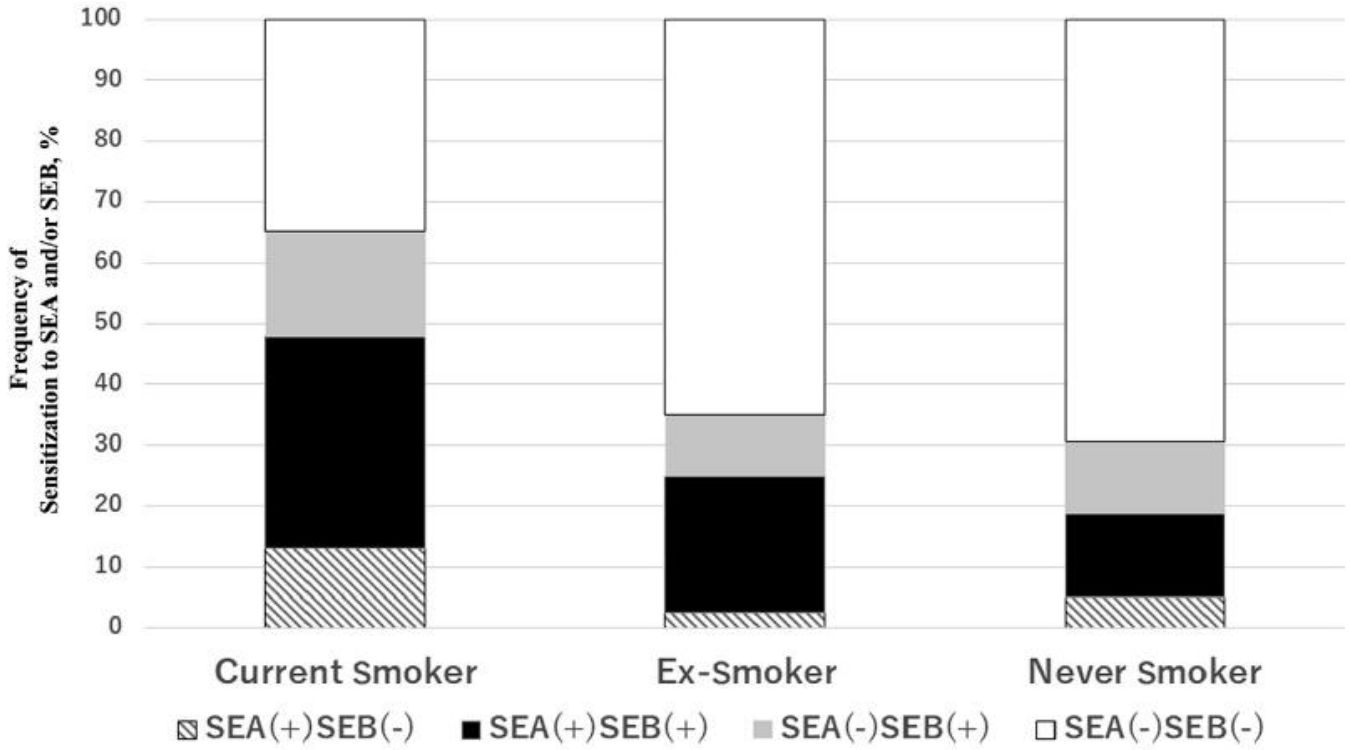

Figure 2. Frequencies of sensitization to *Staphylococcus aureus* enterotoxin A (SEA) and/or *S aureus* enterotoxin B (SEB) in current smokers, ex-smokers, and never smokers with asthma. Plus sign indicates positive; minus sign, negative.

Sensitization to Staphylococcus aureus enterotoxins in smokers with asthma

Tadao Nagasaki, MD, PhD; Ann Allergy Asthma Immunol 119 (2017) 408e414

SEA/SEB ΚΑΙ ΒΡΟΓΧΙΚΗ ΥΠΕΡΑΝΤΙΔΡΑΣΤΙΚΟΤΗΤΑ

Table 1. Demographics of subjects

Parameter	Value
Age, yr	56.1±15.9
sIgE to SE, kU/mL	0.260±0.701
Parameters associated with asthma	
FEV_1, %	76.3±22.1
FEV_1/FVC, %	75.1±11.5
Serum eosinophil, %	349.4±315.7
Sputum eosinophil, %	15.2±18.0
Sex	
Male	22 (27.2)
Female	59 (72.8)
Allergic rhinitis	
Without	20 (24.7)
With	61 (75.3)
Atopy	
Negative	15 (40.5)
Positive	22 (59.5)
Airway hyperresponsiveness	
Negative	24 (54.5)
Positive	20 (45.5)
sIgE to SE (categorized), kU/mL	
<0.10	49 (60.5)
≥0.10	32 (39.5)
Total	81 (100)

Values are presented as mean±standard deviation or number (%). sIgE: specific immunoglobulin E; SE: staphylococcal enterotoxin; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Table 2. Correlation of sIgE to SE with parameters associated with asthma

Parameter	Pearson's coefficient	p-value
FEV_1	0.099	0.385
FEV_1/FVC	0.149	0.206
Serum eosinophil, %	0.091	0.417
Sputum eosinophil, %	0.027	0.815

sIgE: specific immunoglobulin E; SE: staphylococcal enterotoxin; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

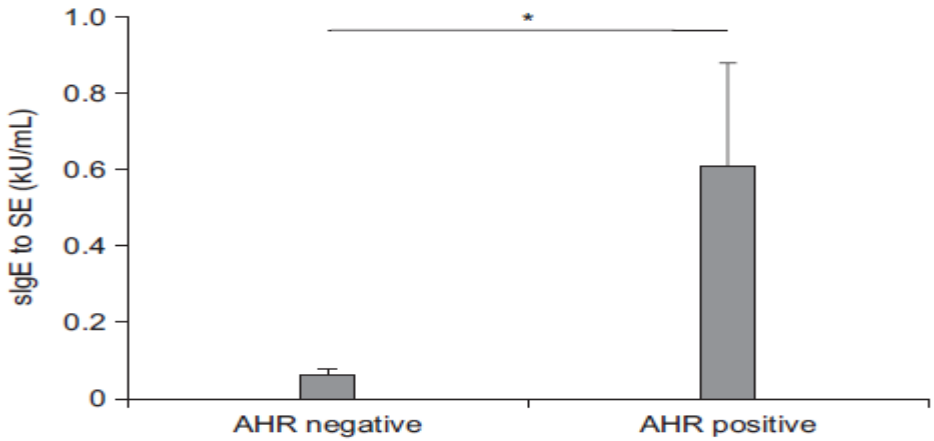

Figure 1. Comparison of specific immunoglobulin E (sIgE) to staphylococcal enterotoxin (SE) levels according to airway hyperresponsiveness (AHR) (p=0.034). *p-value<0.05 obtained by t-test.

Association of Specific Immunoglobulin E to Staphylococcal Enterotoxin with Airway Hyperresponsiveness in Asthma Patients
Seong Han Kim, M.D. Tuberc Respir Dis 2016;79:295-301

SEA/SEB ΚΑΙ ΣΟΒΑΡΟ ΑΣΘΜΑ

TABLE I. Total IgE, IgE antibodies specific to a mixture of inhalant allergens (Phadiatop), IgE antibodies specific to SAE mix, and eosinophil cationic protein in serum of controls, patients with mild asthma, and patients with severe asthma

	Controls (n = 15)	Versus	Mild asthma (n = 34)	Versus	Severe asthma (n = 21)	Versus controls
FEV_1: percent	>80		94 (90-101)		48 (43-57)	
Skin prick test: +/n (%)	(All negative)	$P < .001$	33/34 (97)	$P = .018$	15/21 (71)	$P < .001$
Phadiatop: +/n (%)	3/15 (20)	$P < .001$	33/34 (97)	$P < .001$	9/18 (50)	$P = .155$
SAE mix: +/n (%)	2/15 (13)	$P = .113$	14/34 (41)	$P = .224$	13/21 (62)	$P = .010$
IgE (kU/L)	27 (7-75)	$P < .001$	255 (94-633)	$P = .001$	56 (22-193)	$P = .023$
Eosinophil cationic protein (□g/L)	5.3 (3-8)	$P = .012$	10.4 (6-24)	$P = .290$	16.0 (7-35)	$P = .009$

Skin prick test, Phadiatop, and SAE mix: number of positive cases/total number of cases (percent); statistical analysis, □^{2} test (Yates correction). IgE and eosinophil cationic protein: median (interquartile range); statistical analysis, Mann-Whitney *U* test.

IgE to *Staphylococcus aureus enterotoxins in* serum is related to severity of asthma Letters to the Editor J ALLERGY CLIN IMMUNOL VOLUME 111, NUMBER 5

Staphylococcal enterotoxin-specific IgE: a biomarker for a distinct phenotype of severe asthma?
K. F. Chung et al. Clinical & Experimental Allergy, 46, 387–389
EDITORIAL © 2016 John Wiley & Sons Ltd

SEA/SEB ΚΑΙ ΕΛΕΓΧΟΣ ΑΣΘΜΑΤΟΣ

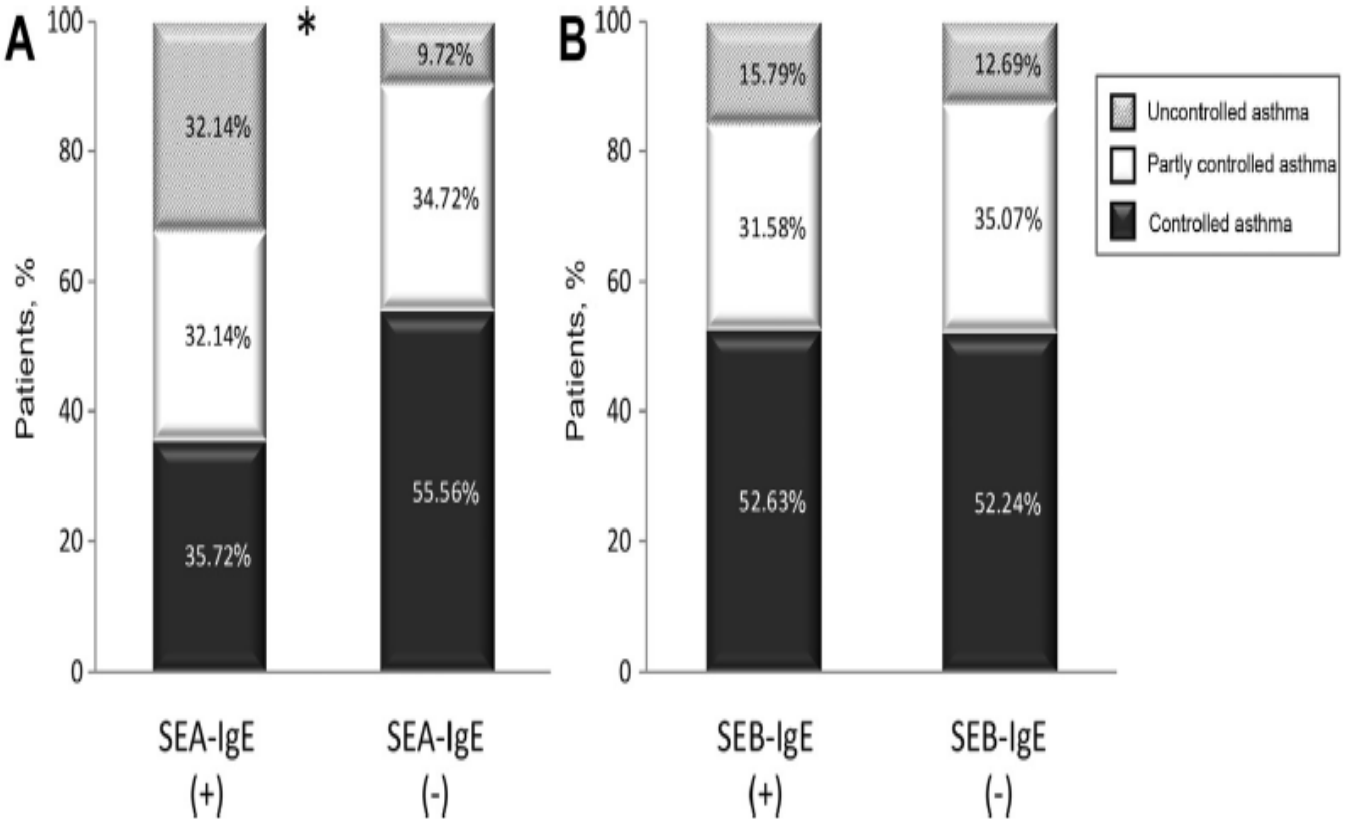

Figure 1. Proportion of asthma control levels in *Staphylococcus aureus* enterotoxin (SE) A–IgE–positive patients and SEA-IgE–negative patients (A) and SEB-IgE–positive patients and SEB-IgE–negative patients (B). *P value given for the χ^2 tests indicates a significant difference ($P = .005$).

Association between specific IgE to Staphylococcus aureus enterotoxins A and B and asthma control

Akihiko Tanaka, MD, PhD et al. Ann Allergy Asthma Immunol 115 (2015) 191e197

ΠΕΙΡΑΜΑΤΙΚΑ ΜΟΝΤΕΛΑ (1)

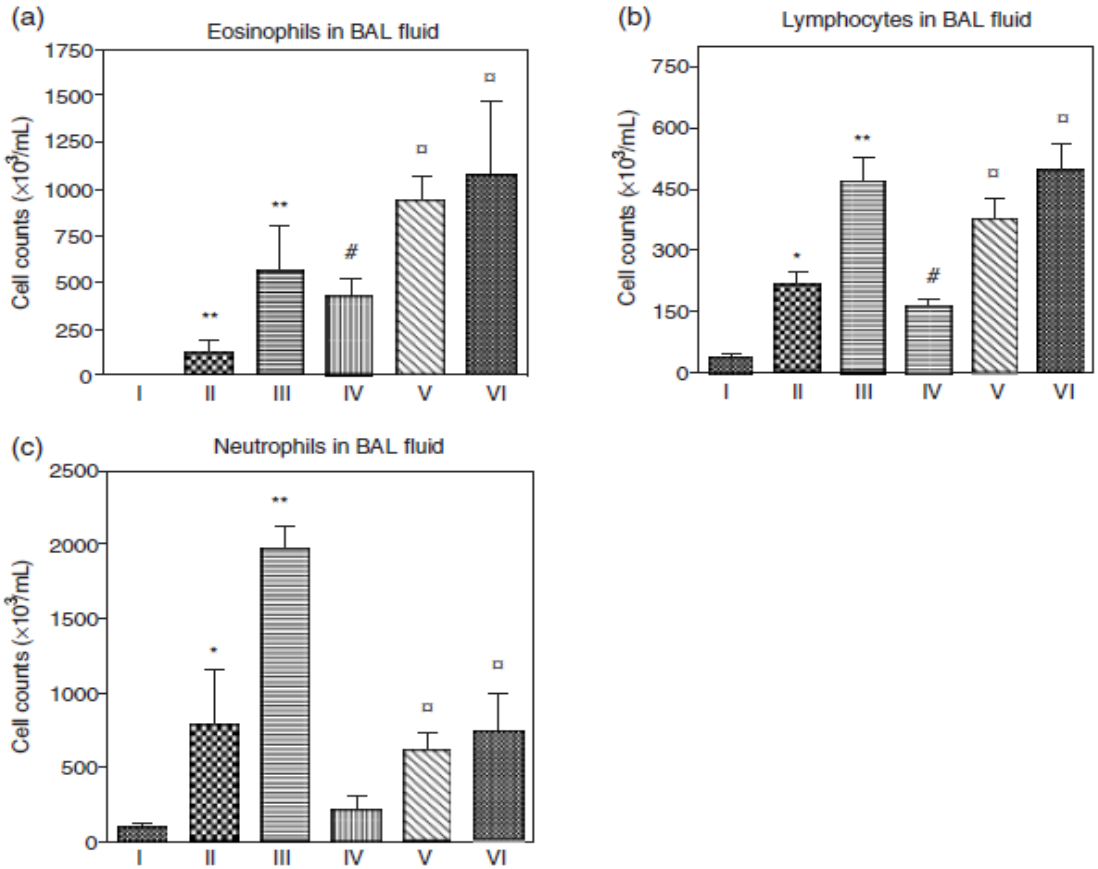

Fig. 2. Effects of nasal or bronchial *Staphylococcus aureus* enterotoxin B (SEB) on differential cell counts in bronchoalveolar lavage (BAL) fluid. In saline (SAL) or ovalbumin (OVA) mice, endonasal or endobronchial application with SAL or SEB was performed during the airway challenge phase (cf. Fig. 1). Differential cell counts were performed on MGG-stained cytospin preparations of BAL fluid cells. Eosinophil (a), lymphocyte (b) and neutrophil (c) counts are expressed in absolute numbers. Each group consisted of six mice. One representative experiment of two is shown. $^{*}P < 0.05$ vs. group I, $^{**}P < 0.05$ vs. group I, $^{\#}P < 0.05$ vs. group I, $^{\S} < 0.05$ vs. group IV.

© 2006 The Authors
Journal compilation © 2006 Blackwell Publishing Ltd, *Clinical and Experimental Allergy*, 36 : 1063–1071

ΠΕΙΡΑΜΑΤΙΚΑ ΜΟΝΤΕΛΑ (1)

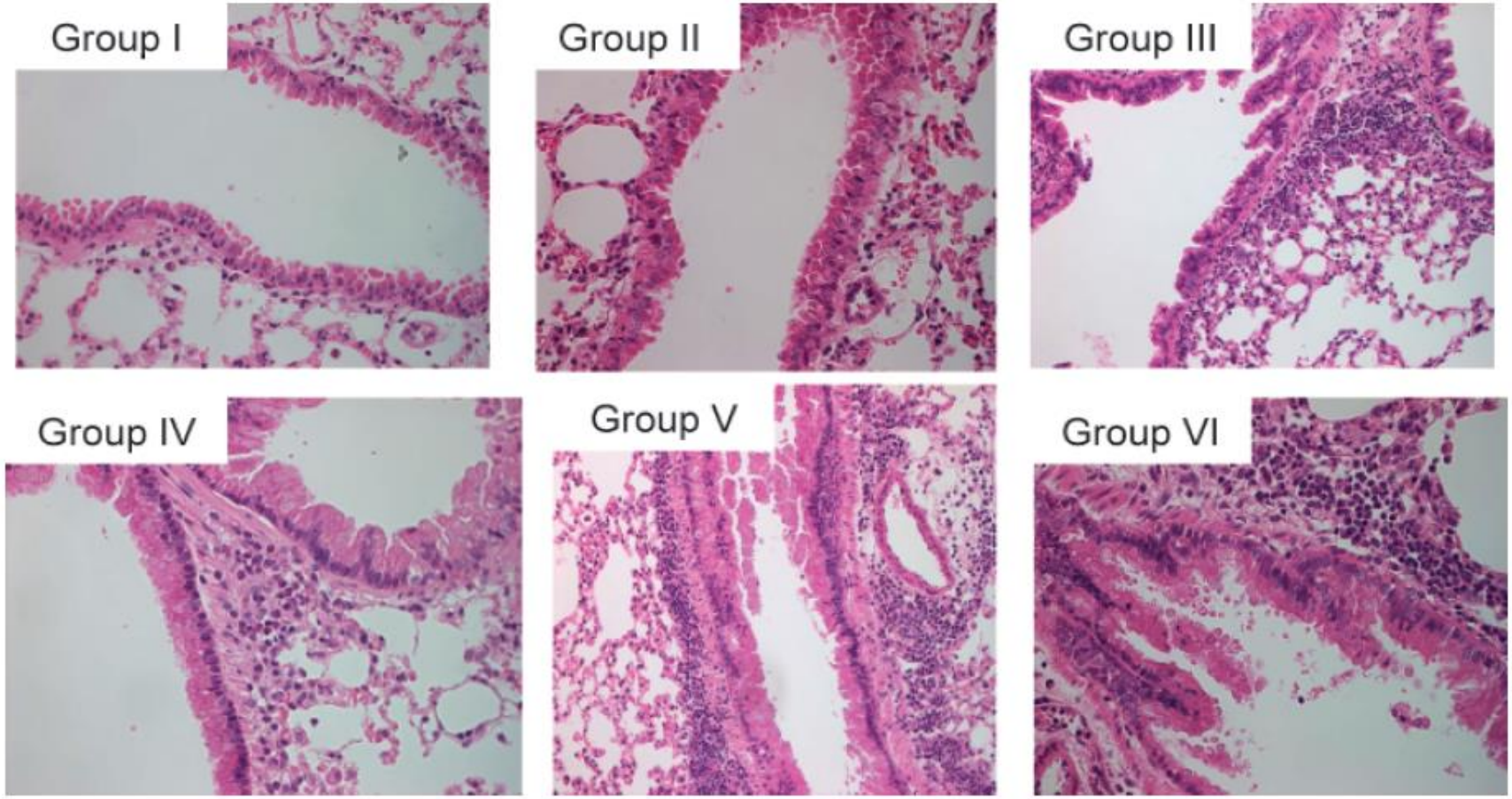

Fig. 3. Histologic sections of peribronchial tissue of sensitized mice repeatedly exposed to aerosols containing saline (SAL; group I until III) or ovalbumin (OVA; group IV until VI). In addition to airway challenges with SAL or OVA, mice had been treated with nasal SEB (II and V) or bronchial SEB (III and VI, cf. Fig. 1). On day 38, mice were killed and peribronchial tissue sections were stained with the classic haematoxylin and eosin stain, allowing the appreciation of peribronchial inflammatory infiltrates.

ΠΕΙΡΑΜΑΤΙΚΑ ΜΟΝΤΕΛΑ(2)

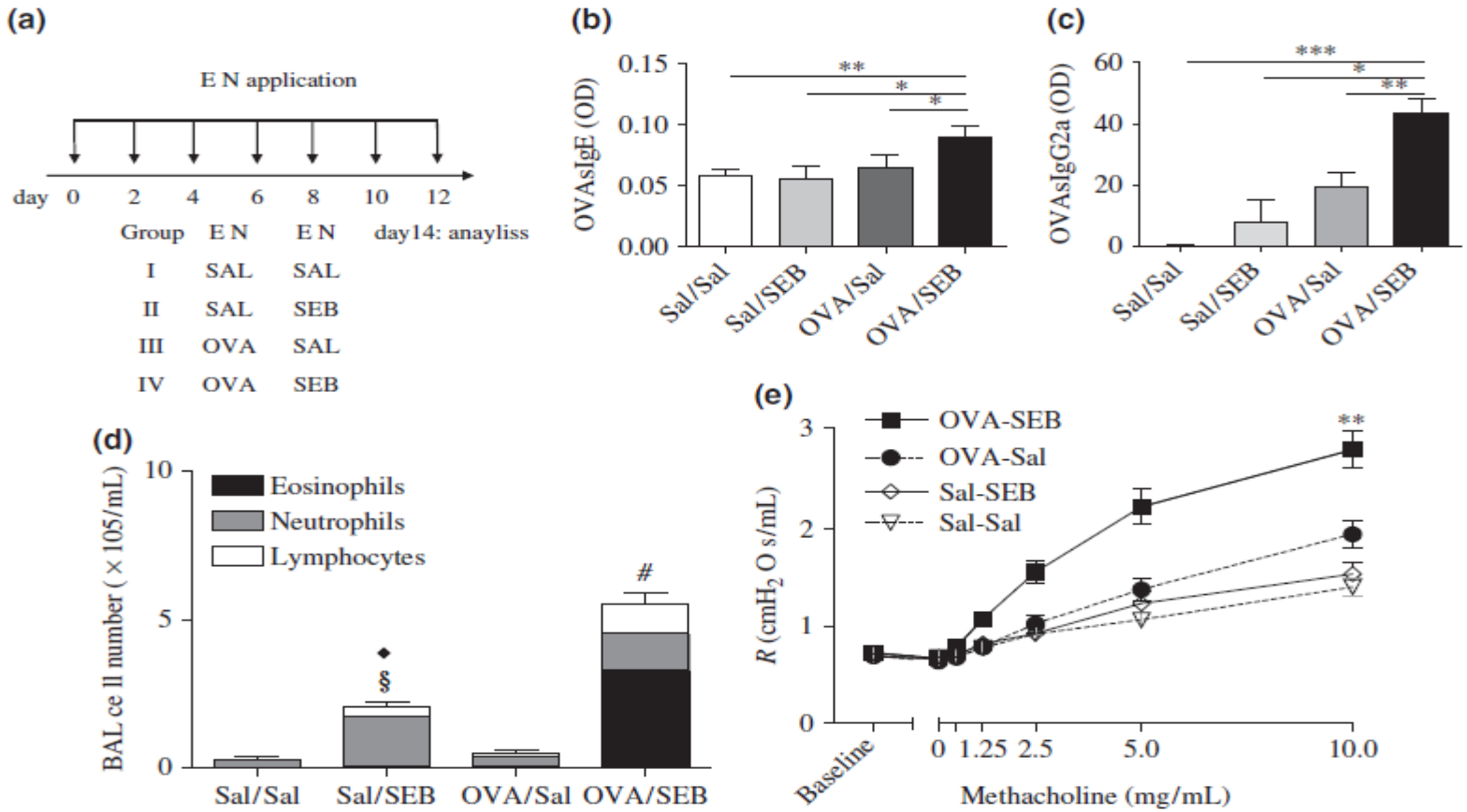

Fig. 2. (b) Concomitant application of OVA and SEB resulted in increased levels of OVA-specific IgE levels, (c) OVA-specific IgG2a levels, (d) BAL eosinophils and lymphocytes and (e) bronchial hyperreactivity measured as resistance (R), compared with the control conditions. One representative experiment out of two is shown. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. $^{\#}P<0.01$ vs. all others (eosinophils) and vs. OVA/Sal and Sal/Sal (lymphocytes). §$P<0.01$ vs. Sal/Sal (neutrophils). $^{\bullet}P<0.05$ vs. Sal/Sal (lymphocytes). OVA, ovalbumin; SEB, *Staphylococcus aureus* Enterotoxin B.

Staphylococcus aureus enterotoxin B facilitates allergic sensitization in experimental asthma
W. Huvenne, et al. Clinical & Experimental Allergy, 40, 1079–1090
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ΝΕΑ ΕΡΕΥΝΗΤΙΚΑ ΜΟΝΤΕΛΑ

- <u>ΜΕΛΕΤΗ:</u>

30 ασθενείς με σοβαρό άσθμα

ΔΕΙΓΜΑΤΑ:

- Ορός
- Πλήρες αίμα
- Προκλητά πτύελα
- BAL
- Βιοψίες πνεύμονα (+ remodeling)

Ποσοτικός προσδιορισμός SEA/SEB στα αντίστοιχα υλικά

ΥΠΟΘΕΤΟΥΜΕ ΠΩΣ:

1. Υπάρχει συσχέτιση μεταξύ σοβαρού άσθματος και εντεροτοξινών SEA και SEB στα διάφορα υλικά που θα εξετασθούν

2. Υπάρχει συγκεκριμένος φλεγμονώδης φαινότυπος στα άτομα με σοβαρό άσθμα που φέρουν τις εντεροτοξίνες καθώς και συγκεκριμένη αναδιαμόρφωση

3. Υπάρχει συγκεκριμένη σωρεία κυτταροκινών στους ασθενείς με σοβαρό άσθμα και εντεροτοξίνες (IL-13 ,TSLP ,ECP, IL-8, INF-γ)

ΣΚΟΠΟΣ:

1. Η μελέτη της συσχέτισης μεταξύ σοβαρού άσθματος και εντεροτοξινών SEA και SEB στα διάφορα υλικά που θα εξετασθούν

2. Η ανάδειξη του φλεγμονώδους φαινοτύπου των πτυέλων που διέπει τα άτομα με σοβαρό άσθμα που φέρουν εντεροτοξίνες

3. Η ανάδειξη των κυτταροκινών που συνυπάρχουν στο σοβαρό άσθμα όταν αυτό συνοδεύεται από αυξημένα επίπεδα εντεροτοξινών (IL-13 ,TSLP ,ECP, IL-8, INF-γ)

4. Η χρήση των αποτελεσμάτων προς ανάδειξη ειδικών θεραπευτικών στόχων στη ρύθμιση του σοβαρού άσθματος

MERCI
THANK YOU
ASANTE
KIA ORA
SPASIBO
MATONDO
JUSPAXAR
MAAKE
MERCI
OBRIGADO
GRAZIE
KIITOS
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