Çocuk ve Adolesan Ağır Astımında Fenotiplendirmede Sorular ve Sorunlar

Cansın Saçkesen

KOÇ ÜNİVERSİTESİ

Plan

- Tanımlama ve eşlik eden durumlar ve ayırıcı tanı
- Ağır ve ağır olmayan astım
- Farklı fenotipler içinde ağır astımı

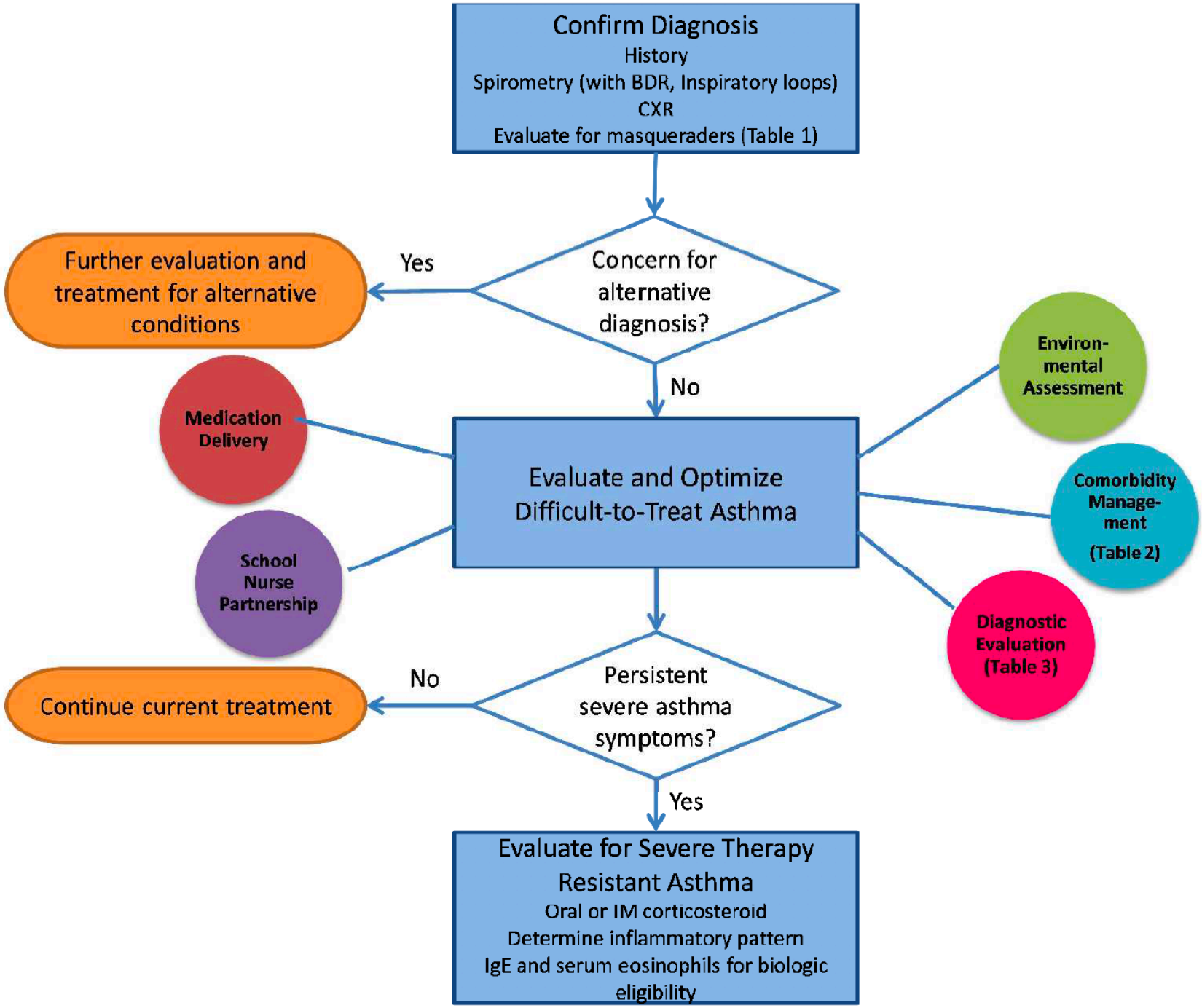
Çocukluk çağı ağır astımı

- Çocukluk çağı astımının %2-5'i ağır astım

- ATS ve ERS tanımına göre ağır astım:
  - Yüksek doz IKS + 2. ajan ve son 1 yılın yarısında sistemik KS
  - Yüksek doz IKS + son 1 yılın yarısında sistemik KS
- Tedavisi ile kontrolsüz → kontrollü astım
- Tedavisi ile halen kontrolsüz astım olarak devam eden

Çocukluk çağı ağır astımı vs Erişkin

- Daha atopik
- Adolesan döneme dek erkek çocuklarda daha sık
- Hava yolu darlığı daha az
- Obezite ile daha az ilişkili



Barsky EE et al. A Practical Approach to Severe Asthma in Children. Ann Am Thorac Soc. 2018 Apr;15(4):399-408.

Ağır astım demeden önce

- Tanı doğru mu?

Barsky EE et al. A Practical Approach to Severe Asthma in Children. Ann Am Thorac Soc. 2018 Apr;15(4):399-408.

Astım ayırıcı tanısı

- Dysfunctional breathing
  - Vocal cord dysfunction
  - Panic attacks
- Anatomic
  - Tracheobronchomalacia
  - Tracheoesophageal fistula
  - Central airway compression or obstruction (e.g. vascular rings, mediastinal mass)
- Suppurative lung diseases
  - Cystic fibrosis
  - Primary ciliary dyskinesia
  - Bronchiectasis
  - Protracted bacterial bronchitis

- Interstitial lung disease
  - Bronchiolitis obliterans
  - Bronchopulmonary dysplasia
- Immune dysfunction/ Rheumatologic disorders
  - Hypogammaglobulinemia
  - Eosinophilic granulomatosis with polyangitis
  - • Connective tissue disease
- Other
  - Foreign body aspiration
  - Chronic aspiration
  - Congenital heart disease

Barsky EE et al. A Practical Approach to Severe Asthma in Children. Ann Am Thorac Soc. 2018 Apr;15(4):399-408.

Ağır astım demeden önce

- Tanı doğru mu?

- Difficult-to treat-asthma mı? (Ağır astımlıların %55'i bu kategoride)
  - Uyum (ilaç uyumu)
  - Doğru teknik
  - Çevresel faktörler
  - Komorbid durumlar

Barsky EE et al. A Practical Approach to Severe Asthma in Children. Ann Am Thorac Soc. 2018 Apr;15(4):399-408.

Komorbid durumlar

- Rhinosinusitis
- Symptomatic GERD
- Vocal cord dysfunction
- Obesity
- Obstructive sleep apnea
- Eosinophilic esophagitis
- Allergic bronchopulmonary aspergillosis
- Psychiatric conditions, such as anxiety and depression

Barsky EE et al. A Practical Approach to Severe Asthma in Children. Ann Am Thorac Soc. 2018 Apr;15(4):399-408.

Ağır astım demeden önce

- Tanı doğru mu?

- Difficult-to treat-asthma mı? (Ağır astımlıların %55'i bu kategoride)
- Uyum (ilaç uyumu)
- Doğru teknik
- Çevresel faktörler
- Komorbid durumlar
- Psikososyal durumlar
- Tanı

Barsky EE et al. A Practical Approach to Severe Asthma in Children. Ann Am Thorac Soc. 2018 Apr;15(4):399-408.

Tanı

Standart

- Pre/post spirometry
- CBC with differential
- IgE
- Specific IgE or skin prick test

İlave

- Inspiratory loops
- Lung Volumes
- Sweat test
- Immunoglobulin levels
- Chest CT
- Sinus CT
- Flexible bronchoscopy
- Direct laryngoscopy
- EGD (ÜST ENDOSKOPİ)
- Polysomnography
- Adrenal insufficiency screening

Barsky EE et al. A Practical Approach to Severe Asthma in Children. Ann Am Thorac Soc. 2018 Apr;15(4):399-408.

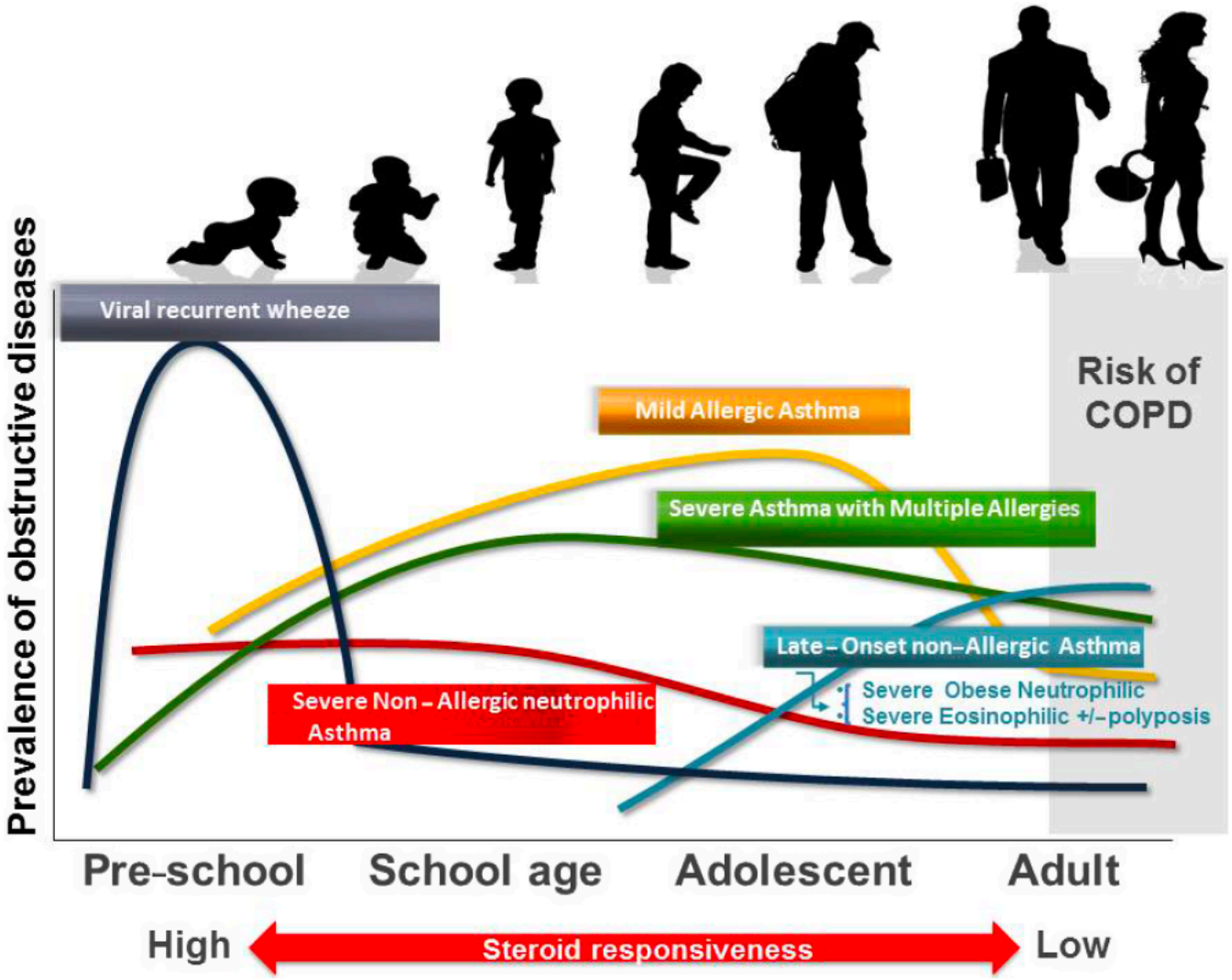
Tedaviye yanıtsız ağır astımda değerlendirme

❑Steroid yanıtı:

- IM Triamcinolone veya oral CS
- Çocukların %20'si ek sistemik steroid dozu ile düzelme, %80'ni kısmi yanıt veriyor
- Yanıt: Semptom, spirometri, inflamatuar belirteçler (FeNO, balgamda eozinofil)

Bossley CJ. Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. The European respiratory journal 2009; 34: 1052-1059.
Severe Asthma Research P. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. American journal of respiratory and critical care medicine 2017; 195: 1439-1448.
Assessment of corticosteroid response in pediatric patients with severe asthma by using a multidomain approach. The Journal of allergy and clinical immunology 2016; 138: 413-420.e416.

Bebeklikten erişkinliğe astım fenotipleri



CEA 2017; 47:848-855

Original Article

Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age

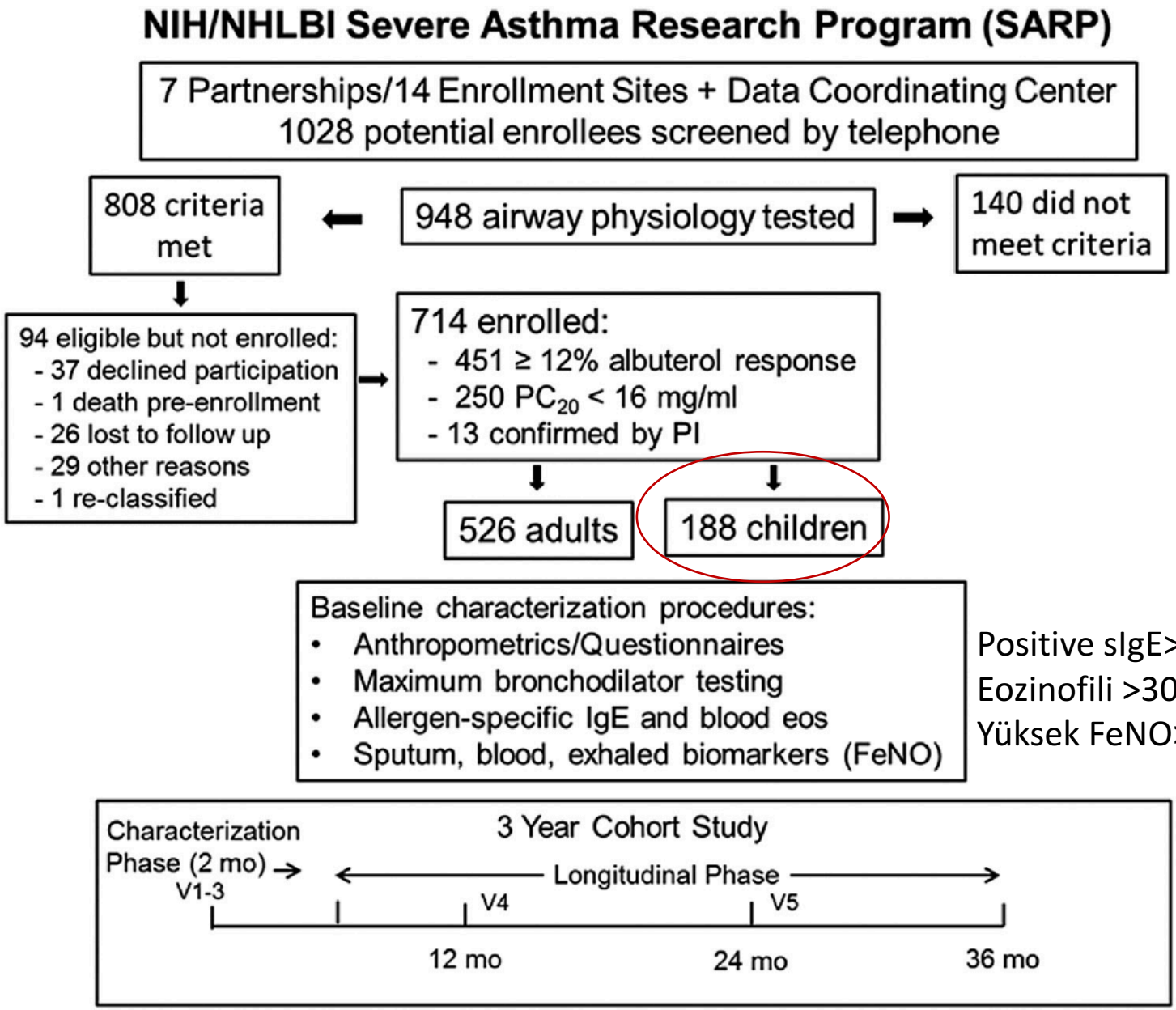
W. Gerald Teague, MD[a], Brenda R. Phillips, MS[b], John V. Fahy, MD, MSc[c], Sally E. Wenzel, MD[d], Anne M. Fitzpatrick, PhD[e], Wendy C. Moore, MD[f], Annette T. Hastie, PhD[f], Eugene R. Bleecker, MD[f], Deborah A. Meyers, PhD[f], Stephen P. Peters, MD, PhD[f], Mario Castro, MD, MPH[g], Andrea M. Coverstone, MD[g], Leonard B. Bacharier, MD[g], Ngoc P. Ly, MD, MPH[c], Michael C. Peters, MD[c], Loren C. Denlinger, MD[h], Sima Ramratnam, MD[h], Ronald L. Sorkness, PhD[h], Benjamin M. Gaston, MD[i], Serpil C. Erzurum, MD[j], Suzy A.A. Comhair, PhD[j], Ross E. Myers, MD[i], Joe Zein, MD[j], Mark D. DeBoer, MD[a], Anne-Marie Irani, MD[k], Elliot Israel, MD[l], Bruce Levy, MD[l], Juan Carlos Cardet, MD[l], Wanda Phipatanakul, MD, MS[l], Jonathan M. Gaffin, MD, MMsc[l], Fernando Holguin, MD, MPH[d], Merritt L. Fajt, MD[d], Shean J. Aujla, MD[d], David T. Mauger, PhD[b], and Nizar N. Jarjour, MD[h] *Charlottesville and Richmond, Va; Hershey and Pittsburgh, Pa; San Francisco, Calif; Atlanta, Ga; Winston-Salem, NC; St. Louis, Mo; Madison, Wis; Cleveland, Ohio; and Boston, Mass*

What is already known about this topic? Severe asthma has distinct phenotypic features in childhood, but whether the features of severe asthma are different with age has not been widely studied.

What does this article add to our knowledge? With advancing age, asthma is more prevalent in women than men, and is associated with higher body mass index and greater airflow limitation, but lower markers of Th2 inflammation.

How does this study impact current management guidelines? Alternate therapies targeting non-Th2 mechanisms of inflammation need further study in the management of adult patients with severe asthma.

JACI in Practice 2018;6:545-54



Positive sIgE>0.35 kU/L
Eozinofili >300 hücre/μL
Yüksek FeNO>30 ppb

JACI in Practice 2018;6:545-54

	Children (<18 y)	
	Severe	Nonsevere
Sample, n	111	77
Age at enrollment (y), mean ± SD	11.5 ± 2.8	11.6 ± 2.9
Female, n (%)†	44 (39.6)	27 (35.1)
Race/ethnicity, n (%)		
Caucasian	39 (35.1)	33 (42.9)
African American	49 (44.1)	32 (41.6)
Other	23 (20.7)	12 (15.6)
Hispanic	17 (15.3)	11 (14.3)
Non-Hispanic	94 (84.7)	66 (85.7)
BMI (kg/m^2), mean ± SD	23.3 ± 6.5	22.3 ± 5.8
Obese		
BMI ≥ 30 (18+ y) or BMI ≥ 95th percentile (<18 y), n (%)	42 (37.8)	23 (29.9)
Smoking history in adults ≥30 y (pack years), mean ± SD	n/a	n/a
Asthma symptom control		
ACT ≤ 19 (≥12 y), n (%)	29* (72.5)	8 (26.7)
cACT ≤ 19 (age 6-11), n (%)	51 (71.8)*	18 (38.3)
ACQ(6), mean ± SD	1.3 ± 0.9*	0.9 ± 0.8
Age of asthma diagnosis (y), mean ± SD	3.0 ± 2.7	3.2 ± 2.8
Years since onset of asthma symptoms, mean ± SD	8.4 ± 3.4	8.4 ± 3.8
Years since asthma diagnosis, mean ± SD	9.1 ± 3.2	9.3 ± 3.4
Number of exacerbations, mean ± SD (past 12 mo)	2.8 ± 2.9*	0.8 ±1.0
Total AQLQ(S) score (≥12 y), mean ± SD	n/a	n/a
Total PAQLQ(S) (age 6-11), mean ± SD	4.9 ± 1.3	5.8 ± 1.1
Number controller medications, median (IQR)	3.0 (2.0, 3.0)*	2.0 (1.0, 2.0)
Daily oral corticosteroids current, n (%)	15 (13.5)*	1 (1.3)
Medication Adherence Report Scale (MARS-5)‡, mean ± SD	21.9 ± 2.9	21.4 ± 3.7

Her 2 grupta:
Erkekler ↑

Ağır grupta
Semptom ↑
Alevlenme ↑
Hayat kalitesi↓
İlaç sıklığı ↑
Prednisone ↑
Obezite daha sık değil

JACI in Practice 2018;6:545-54

Solunum fonksiyon testleri

	Children (<18 y)	
	Severe	Nonsevere
Sample, n	111	77
Pre-BD FEV_1 (% pred.), mean ± SD	87.3 ± 17.7*	93.2 ± 14.3
Mean *Z* score ± SD†	−1.0 ± 1.4*	−0.5 ± 1.1
Pre-BD FVC (% pred.), mean ± SD	101.5 ± 15.6	105.0 ± 13.3
Mean *Z* score ± SD	0.1 ± 1.3	0.4 ± 1.1
Pre-BD FEV_1/FVC (% pred.), mean ± SD	85.3 ± 11.1*	88.4 ± 9.6
Mean *Z* score ± SD	−1.8 ± 1.2*	−1.4 ± 1.0
Pre-BD FEV_1/FVC < LLN‡, n (%)	61.0 (55.0)*	31.0 (40.3)
Maximum post-BD FEV_1 (% pred.), mean ± SD	103.4 ± 17.5	105.6 ± 13.4
Mean *Z* score ± SD	0.3 ± 1.4	0.5 ± 1.1
Maximum post-BD FEV_1/FVC (% pred.), mean ± SD	95.1 ± 8.7	96.4 ± 7.4
Mean *Z* score ± SD	−0.6 ± 1.2	−0.4 ± 1.0
Maximum post-BD FEV_1/FVC < LLN, n (%)§	18.0 (16.2)	13.0 (16.9)
FEV_1 BD response (absolute change), mean ± SD	16.2 ± 11.0*	12.4 ± 7.8

Ağır grupta:

Pre-BD hava yolu obs daha fazla

Post-BD hava yolu obs daha ağır olmayan grup ile benzer

Post-BD FEV1% predicted değişimi fazla

JACI in Practice 2018;6:545-54

İnflamatuar belirteçler ve Allerjen sensitizasyonu

	Children (<18 y)	
	Severe	Nonsevere
Sample, n	111	77
Sputum differential, n	27	17
Sputum cell count (cells × 10^4/μL), median (min, max)	77.4 (23.7, 153.1)	61.9 (9.5, 199.8)
Sputum eosinophil %, median (min, max)	1.6 (0.0, 53.7)	1.1 (0.0, 61.4)
Sputum neutrophil %, median (min, max)	53.8 (9.4, 90.1)	40.8 (8.3, 80.3)
FeNO (ppb), median (quartiles)	23.0 (12.0, 46.0)	28.0 (12.0, 49.0)
Expired NO > 30 ppb, n (%)†	40 (36.7)	33 (44.0)
Serum IgE, median (quartiles)	465 (164, 1207)	490 (151, 834)
At least 1 of 15 positive blood IgE tests, n (%)	104 (94.5)	67 (89.3)
Number of positive (of 15) allergen-specific IgE tests, median (min, max)	6.0 (3.0, 11.0)	7.0 (3.0, 11.0)
Highly sensitized ≥ 4/15 positive allergen tests, n (%)	74 (67.3)	50 (66.7)
Blood eosinophils (%), median (quartiles)	5.4 (2.5, 9.0)	5.6 (3.5, 8.3)
Total blood eosinophils (cells/μL), median (quartiles)	324 (162, 514)	359 (208, 575)
Blood eosinophilia ≥300 cells/μL, n (%)	60 (54.1)	49 (63.6)

Hiçbir parametrede farklılık yok

JACI in Practice 2018;6:545-54

Erişkinlerde ise

❑Ağır ve Ağır olmayan

- Her 2 grupta kadın ağırlıklı
- Ağır astım'da yaş ↑, BMI ↑, semptom ↑, astım süresi ↑, hayat kalitesi↓
- Uyum ve tanı yaşı her 2 grupta benzer

- Ağır grupta pre- ve post-BD obst ↑
- Ağır grupta Post-BD FEV1% pred değişimi ↑

- Ağır olmayan astım grubunda FeNO ↑
- Ağır astım'da eosinofil ↑ ve eozinofili (>300 hücre/μL) olgu sayısı ↑
- Ağır astımda positif sIgE yanıtı ↓

ORIGINAL ARTICLE

Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations

Loren C. Denlinger[1], Brenda R. Phillips[2], Sima Ramratnam[1], Kristie Ross[3], Nirav R. Bhakta[4], Juan Carlos Cardet[5], Mario Castro[6], Stephen P. Peters[7], Wanda Phipatanakul[5], Shean Aujla[8], Leonard B. Bacharier[6], Eugene R. Bleecker[7], Suzy A. A. Comhair[9], Andrea Coverstone[6], Mark DeBoer[10], Serpil C. Erzurum[9], Sean B. Fain[1], Merritt Fajt[8], Anne M. Fitzpatrick[11], Jonathan Gaffin[5], Benjamin Gaston[3], Annette T. Hastie[7], Gregory A. Hawkins[7], Fernando Holguin[8], Anne-Marie Irani[12], Elliot Israel[5], Bruce D. Levy[5], Ngoc Ly[4], Deborah A. Meyers[7], Wendy C. Moore[7], Ross Myers[3], Maria Theresa D. Opina[7], Michael C. Peters[4], Mark L. Schiebler[1], Ronald L. Sorkness[1], W. Gerald Teague[10], Sally E. Wenzel[8], Prescott G. Woodruff[4], David T. Mauger[2], John V. Fahy[4], and Nizar N. Jarjour[1]; for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program-3 Investigators

[1]University of Wisconsin, Madison, Wisconsin; [2]The Pennsylvania State University College of Medicine, Hershey, Pennsylvania; [3]Case Western Reserve University, Cleveland, Ohio; [4]University of California San Francisco, San Francisco, California; [5]Harvard Medical School, Boston, Massachusetts; [6]Washington University, St. Louis, Missouri; [7]Wake Forest University, Winston-Salem, North Carolina; [8]University of Pittsburgh, Pittsburgh, Pennsylvania; [9]The Cleveland Clinic, Cleveland, Ohio; [10]University of Virginia, Charlottesville, Virginia; [11]Emory University, Atlanta, Georgia; and [12]Virginia Commonwealth University, Richmond, Virginia

Abstract

Rationale: Reducing asthma exacerbation frequency is an important criterion for approval of asthma therapies, but the clinical features of exacerbation-prone asthma (EPA) remain incompletely defined.

Objectives: To describe the clinical, physiologic, inflammatory, and comorbidity factors associated with EPA.

Methods: Baseline data from the NHLBI Severe Asthma Research Program (SARP)-3 were analyzed. An exacerbation was defined as a burst of systemic corticosteroids lasting 3 days or more. Patients were classified by their number of exacerbations in the past year: none, few (one to two), or exacerbation prone (≥3). Replication of a multivariable model was performed with data from the SARP-1 + 2 cohort.

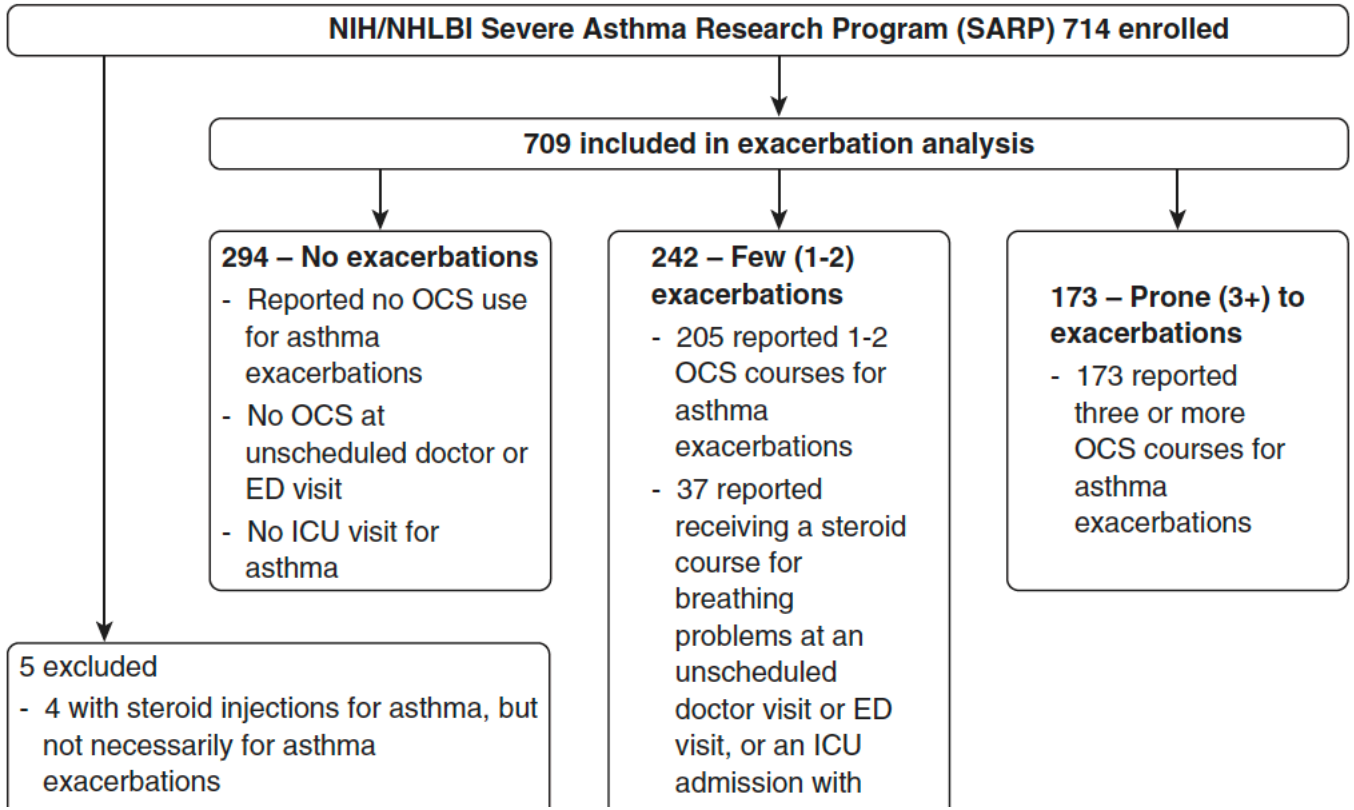
Measurements and Main Results: Of 709 subjects in the SARP-3 cohort, 294 (41%) had no exacerbations and 173 (24%) were exacerbation prone in the prior year. Several factors normally associated with severity (asthma duration, age, sex, race, and socioeconomic status) did not associate with exacerbation frequency in SARP-3; bronchodilator responsiveness also discriminated exacerbation proneness from asthma severity. In the SARP-3 multivariable model, blood eosinophils, body mass index, and bronchodilator responsiveness were positively associated with exacerbation frequency (rate ratios [95% confidence interval], 1.6 [1.1–2.1] for every log unit of eosinophils, 1.3 [1.1–1.4] for every 10 body mass index units, and 1.2 [1.1–1.4] for every 10% increase in bronchodilatory responsiveness). Chronic sinusitis and gastroesophageal reflux were also associated with exacerbation frequency (1.7 [1.4–2.1] and 1.6 [1.3–2.0]), even after adjustment for multiple factors. These effects were replicated in the SARP-1 + 2 multivariable model.

Conclusions: EPA may be a distinct susceptibility phenotype with implications for the targeting of exacerbation prevention strategies.

Clinical trial registered with www.clinicaltrials.gov (NCT 01760915).

Keywords: exacerbation-prone asthma; bronchodilator reversibility; eosinophils; sinusitis; gastroesophageal reflux

AJRCCM 2017;195:302



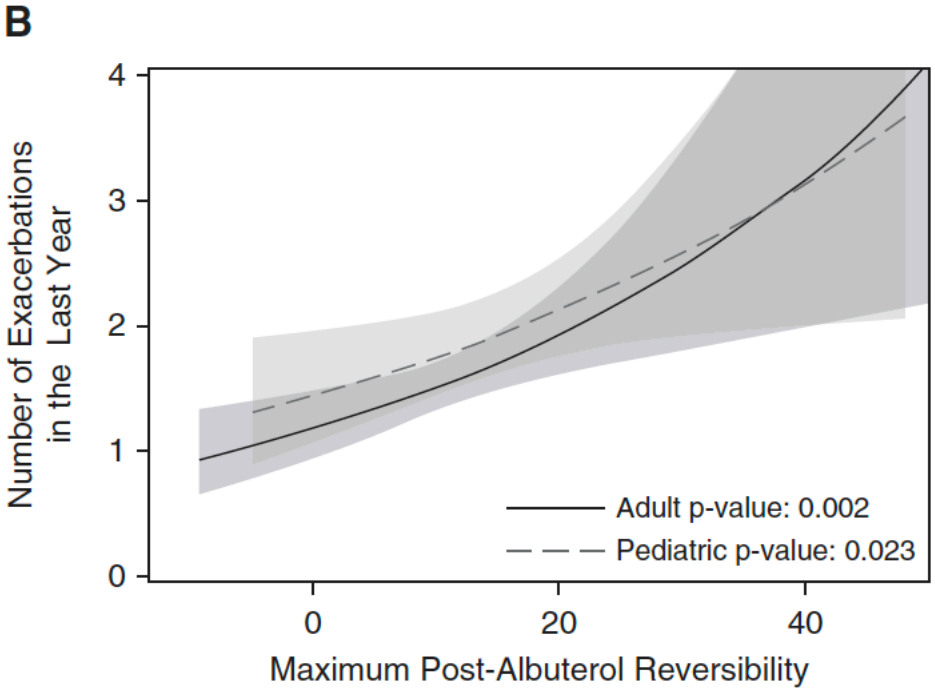
	Number of Systemic Corticosteroid Bursts			
	None	Few (*1–2*)	Prone (⩾*3*)	*P* Value
N	294	242	173	
Severe asthma, n (%),* CS	110 (37)	157 (65)	152 (88)	<0.001
Asthma duration, yr, median (IQR)	24 (12–38)	19 (10–37)	19 (9–39)	0.208
Adults (⩾18)				
N (column %, row %)	236 (80, 45)	163 (67, 31)	123 (71, 24)	—
Age, yr, median (IQR),* KW	47 (33–55)	50 (38–58)	52 (41–60)	0.003
Adolescents (12–18)				
N (column %, row %)	29 (10, 41)	21 (9, 30)	21 (12, 30)	—
Age, yr, median (IQR)	15 (13–16)	14 (14–15)	14 (13–15)	0.155
Children (6–11)				
N (column %, row %),* CS Bonferroni	29 (10, 25)	58 (24, 50)	29 (17, 25)	—
Age, yr, median (IQR)	10 (9–11)	10 (9–11)	9 (8–10)	0.108
Female sex, n (%)	166 (57)	152 (63)	104 (60)	0.323

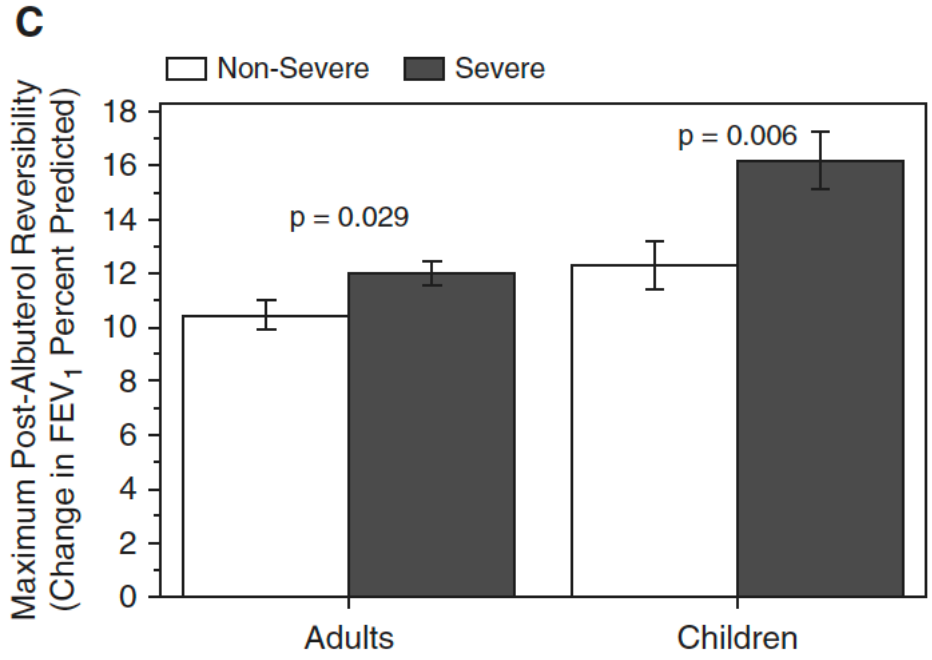
Solunum Fonksiyon Testleri

	Number of Systemic Corticosteroid Bursts			
	None (*Children: n = 58; Adults: n = 236*)	Few (*1–2*) (*Children: n = 79; Adults: n = 163*)	Prone (⩾*3*) (*Children: n = 50; Adults: n = 123*)	*P* Value
FEV_1 /FVC				
Children,* LR				
Ratio	0.78 ± 0.09	0.76 ± 0.09	0.75 ± 0.1	0.091
z score	−1.34 ± 0.97	−1.67 ± 1.17	−1.81 ± 1.20	0.072
Adults,* LR				
Ratio	0.70 ± 0.09	0.69 ± 0.11	0.65 ± 0.13	<0.001
z score	−1.62 ± 1.10	−1.60 ± 1.29	−1.93 ± 1.51	0.050
FEV_1				
Children,* LR				
% Predicted	94.09 ± 13.24	88.87 ± 16.70	86.16 ± 19.08	0.036
z score	−0.48 ± 1.06	−0.87 ± 1.30	−1.07 ± 1.45	0.046
Adults,* LR				
% Predicted	76.79 ± 18.73	72.26 ± 20.12	63.96 ± 21.52	<0.001
z score	−1.62 ± 1.28	−1.89 ± 1.34	−2.50 ± 1.44	<0.001
FVC				
Children				
% Predicted	105.24 ± 11.61	102.72 ± 15.86	100.50 ± 16.23	0.245
z score	0.43 ± 0.95	0.22 ± 1.28	0.04 ± 1.34	0.245
Adults,* LR				
% Predicted	88.97 ± 17.18	83.92 ± 17.40	77.45 ± 17.57	<0.001
z score	−0.79 ± 1.26	−1.14 ± 1.27	−1.65 ± 1.31	<0.001
Postalbuterol change in FEV_1% predicted				
Children,* LR	11.40 ± 8.46	16.13 ± 10.31	15.93 ± 10.51	0.012
Adults	10.73 ± 7.66	11.27 ± 8.01	12.73 ± 8.07	0.073
FEV_1 ⩾80% predicted, n (row %, column %)				
Children (n = 139)	48 (34.5, 83)	58 (41.7, 73)	33 (23.7, 66)	0.135
Adults (n = 189),* CS	104 (55.0, 44)	59 (31.2, 36)	26 (13.7, 21)	<0.001
FEV_1 <60% predicted, n (row %, column %)				
Children (n = 6)	0 (0, 0)	3 (50, 4)	3 (50, 6)	0.195
Adults (n = 137),* CS	40 (29, 17)	42 (31, 26)	55 (40, 45)	<0.001

Alevlenme ile reversibilite yanıtı arasında pozitif ilgi

Ağır astım ile reversibilite yanıtı (>%12) arasında pozitif ilgi





AJRCCM 2017;195:302

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Childhood Allergic Asthma Is Not a Single Phenotype

Jocelyne Just, MD, PhD[1], Philippe Saint-Pierre, PhD[2], Rahele Gouvis-Echraghi, MD[1], Yacine Laoudi, MD[1], Layde Roufai, MD[1], Isabelle Momas, PharmD, PhD[3], and Isabella Annesi Maesano, MD, PhD, DSc[4]

Trousseau Asthma Program (TAP)

6-12 yaş astımlı çocuklar

cluster analysis:

(1)sex and age;

(2) allergic rhinitis, eczema, and food allergy

(3) Asthma duration, asthma severity, and asthma control, thresholds for high-dose were defined as 500 mcg fluticasone (or its equivalent)/day. Hospitalization for severe exacerbation

(4) FVC, FEV1 , FEF25-75

(5) blood eosinophilia, total IgE;

(6) Allergic sensitization Multiple sensitizations were defined as more than 2 sensitizations to inhaled allergens;

(7) fractional exhaled nitric oxide (FeNO)

J Pediatr 2014;164:815-20.

Table I. Characteristics of children according to cluster analysis in the entire population (n = 125)

	Total cohort (n = 125)	Cluster 1 "*Multiple Allergies and Severe Asthma*" (n = 20)	Cluster 2 "*Pollen Sensitization with Severe Exacerbations*" (n = 12)	Cluster 3 "*Multiple Allergic Sensitizations and Mild Asthma*" (n = 36)	Cluster 4 "*HDM Sensitization and Mild Asthma*" (n = 57)	*P* value*
Male sex n (%)	85 (68)	15 (75)	**11 (92)**	28 (78)	31 (54)	**.018**
Age (y)	8.9 ± 2.6	9.3 ± 2.2	8.9 ± 2.8	**10** ± 2.6	8.3 ± 2.4	**.016**
Asthma duration (y)	5.5 ± 3.2	6.8 ± 2.9	5.0 ± 3.1	5.6 ± 3.1	5.1 ± 3.3	.136
Eczema n (%)	58 (46)	**18 (90)**	6 (50)	14 (39)	20 (35)	**<.001**
Food allergy n (%)	13 (10)	1 (5)	**4 (33)**	6 (17)	2 (4)	**.013**
Asthma severity† n (%)						
Moderate to severe asthma	46 (37)	**19 (95)**	11 (92)	1 (3)	15 (26)	**<.001**
≥1 hospitalization for asthma exacerbation	26 (21)	7 (35)	**11 (92)**	0 (0)	8 (14)	**<.001**
Controlled without high-dose of ICS	10 (8)	0 (0)	**0 (0)**	5 (14)	5 (9)	
Uncontrolled with high-dose of ICS	7 (6)	2 (10)	**1 (8)**	1 (3)	3 (5)	.173
Serum total IgE (kU/L)	688 ± 962	**1123** ± 1344	601 ± 410	581 ± 545	622 ± 1066	**.006**
Specific IgE n (%) against						
multiple allergens	61 (49)	**20 (100)**	5 (42)	35 (97)	1 (2)	**<.001**
HDM	96 (77)	**19 (95)**	3 (25)	32 (89)	42 (74)	**<.001**
Pollens	47 (38)	12 (60)	**11 (92)**	20 (56)	4 (7)	**<.001**
Cat or dog dander	45 (36)	**14 (70)**	2 (17)	25 (69)	4 (7)	**<.001**
Mold	15 (12)	4 (20)	0 (0)	**11 (31)**	0 (0)	**<.001**
Functional parameters						
FVC (% pred)	97.8 ± 11.8	97.9 ± 13.6	94 ± 10.3	99.8 ± 10.7	97.3 ± 12.2	.701
FEV_1 (% pred)	97.6 ± 12.4	91.6 ± 17.2	98.4 ± 10.1	101.6 ± 10.8	97 ± 11.1	.182
$FEF_{25\%-75\%}$ (% pred)	84.3 ± 25.9	**71** ± 34	95.1 ± 21.6	90.2 ± 18.6	82.7 ± 26.2	**.009**
FeNO (ppb)	53.4 ± 27	**67.3** ± 30	56.5 ± 27.5	55.5 ± 24.7)	46.6 ± 25.7	**.031**

J Pediatr 2014;164:815-20.

Çevresel faktörler: küf mantarı maruziyeti ağır astım ile ilgili

Table II. Environmental features of children according to cluster analysis in the entire population (n = 125)

	Total Cohort (n = 125)	Cluster 1 "*Multiple Allergies and Severe Asthma*" (n = 20)	Cluster 2 "*Pollen Sensitization with Severe Exacerbations*" (n = 12)	Cluster 3 "*Multiple Allergic Sensitizations and Mild Asthma*" (n = 36)	Cluster 4 "*HDM Sensitization and Mild Asthma*" (n = 57)	*P* value*
Tobacco smoke exposure n (%)	40 (32)	4 (20)	2 (17)	10 (28)	22 (39)	.428
Mold exposure n (%)	24 (19)	**9 (45)**	5 (42)	1 (3)	11 (19)	**.004**
Cockroaches exposure n (%)	9 (7)	1 (5)	1 (8)	4 (11)	3 (5)	.743
Furred pet exposure n (%)	27 (22)	6 (30)	2 (17)	9 (25)	10 (18)	.521

J Pediatr 2014;164:815-20.

TAP Study

Ağır astım

- >2 sensitization

HDM>Pollen>Cat/Dog

- Eczema (90%)
- FEF25-75↓: aver 71%
- tIgE ↑ : 1123 kU/L
- FeNO ↑: 67.3 ppb
- Mould exposure

Ağır alevlenmeler

- >2 sensitization

  Pollen
- Food allergy (33%)

Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies

Danielle C M Belgrave, Raquel Granell, Steve W Turner, John A Curtin, Iain E Buchan, Peter N Le Souëf, Angela Simpson, A John Henderson*, Adnan Custovic**

Summary

Background Maximal lung function in early adulthood is an important determinant of mortality and COPD. We investigated whether distinct trajectories of lung function are present during childhood and whether these extend to adulthood and infancy.

Methods To ascertain trajectories of FEV_1, we studied two population-based birth cohorts (MAAS and ALSPAC) with repeat spirometry from childhood into early adulthood (1046 participants from 5–16 years and 1390 participants from 8–24 years). We used a third cohort (PIAF) with repeat lung function measures in infancy (V'_{maxFRC}) and childhood (FEV_1; 196 participants from 1 month to 18 years of age) to investigate whether these childhood trajectories extend from early life. We identified trajectories using latent profile modelling. We created an allele score to investigate genetic associations of trajectories, and constructed a multivariable model to identify their early-life predictors.

Findings We identified four childhood FEV_1 trajectories: persistently high, normal, below average, and persistently low. The persistently low trajectory (129 [5%] of 2436 participants) was associated with persistent wheezing and asthma throughout follow-up. In genetic analysis, compared with the normal trajectory, the pooled relative risk ratio per allele was 0·96 (95% CI 0·92–1·01; p=0·13) for persistently high, 1·01 (0·99–1·02; p=0·49) for below average, and 1·05 (0·98–1·13; p=0·13) for persistently low. Most children in the low V'_{maxFRC} trajectory in infancy did not progress to the low FEV_1 trajectory in childhood. Early-life factors associated with the persistently low trajectory included recurrent wheeze with severe wheezing exacerbations, early allergic sensitisation, and tobacco smoke exposure.

Interpretation Reduction of childhood smoke exposure and minimisation of the risk of early-life sensitisation and wheezing exacerbations might reduce the risk of diminished lung function in early adulthood.

Lancet Respir Med 2018

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http://dx.doi.org/10.1016/S2213-2600(18)30141-3

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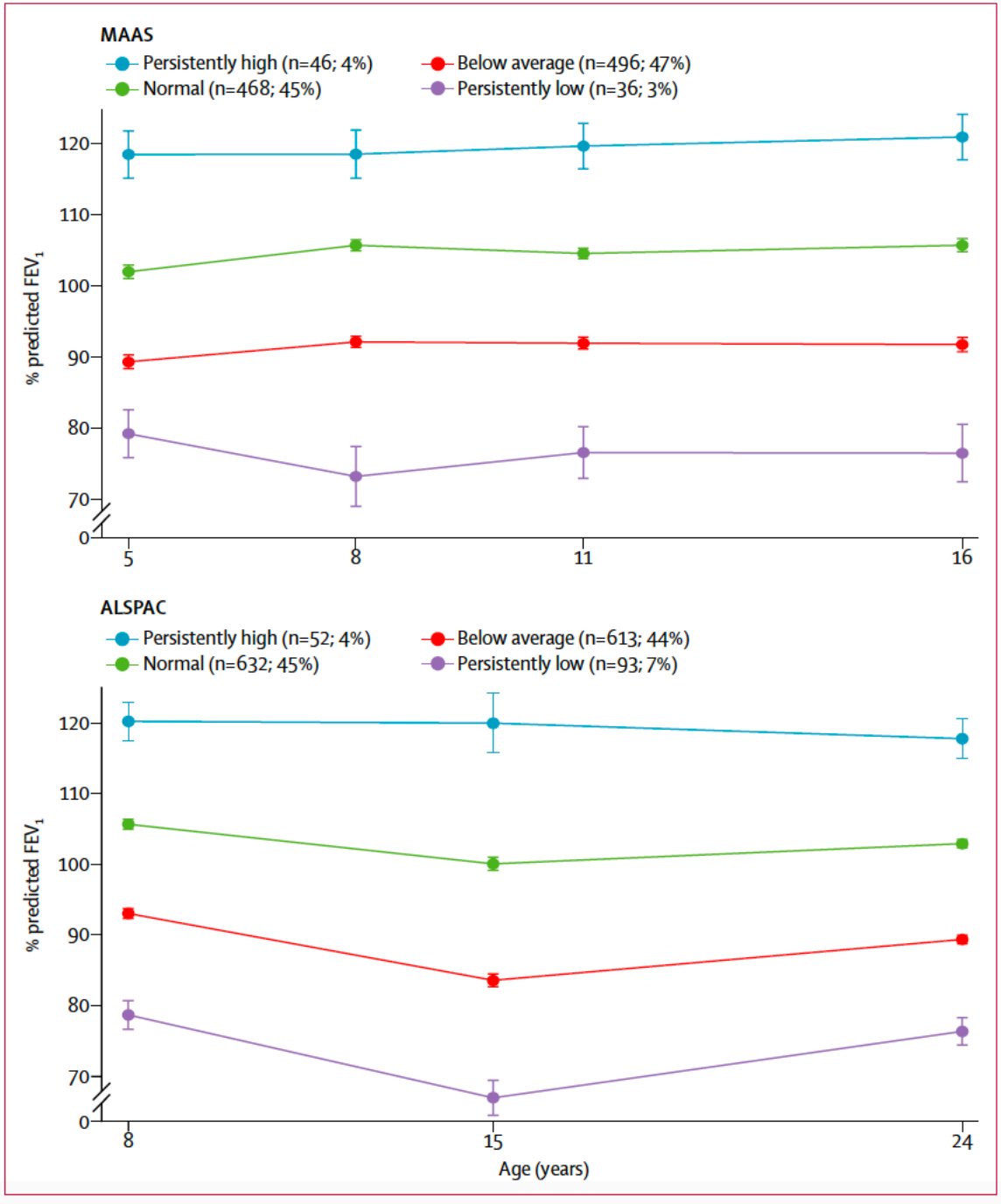
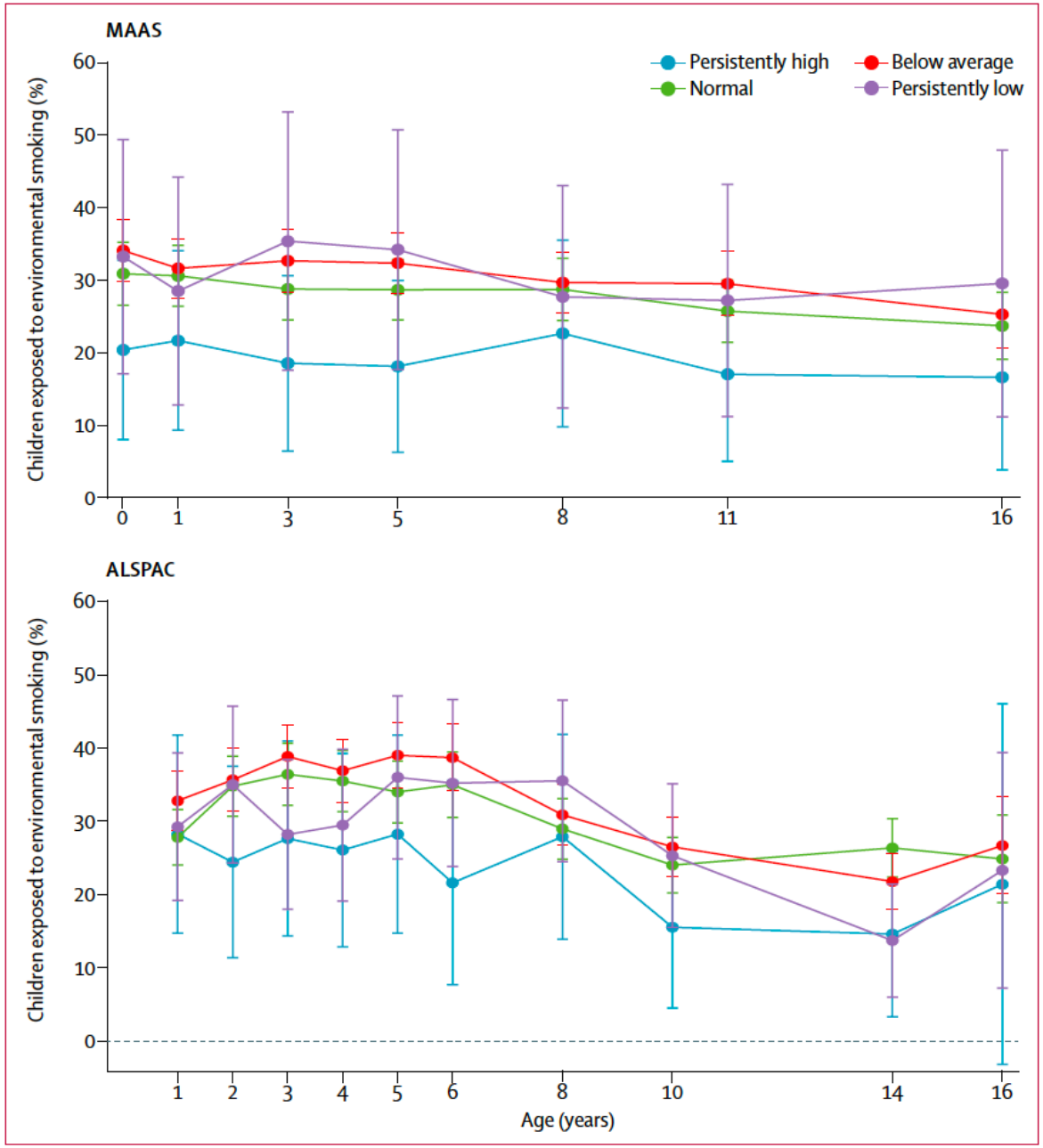


Persistently high (n=46; 4%)
Normal (n=468; 45%)
Below average (n=496; 47%)
Persistently low (n=36; 3%)

Persistently high (n=52; 4%)
Below average (n=613; 44%)
Normal (n=632; 45%)
Persistently low (n=93; 7%)

Sigara maruziyeti FEV1 düşük olanlarda daha yüksek oranlarda



MAS Cohort:
Persistan düşük FEV1 vs Persistan yüksek FEV1

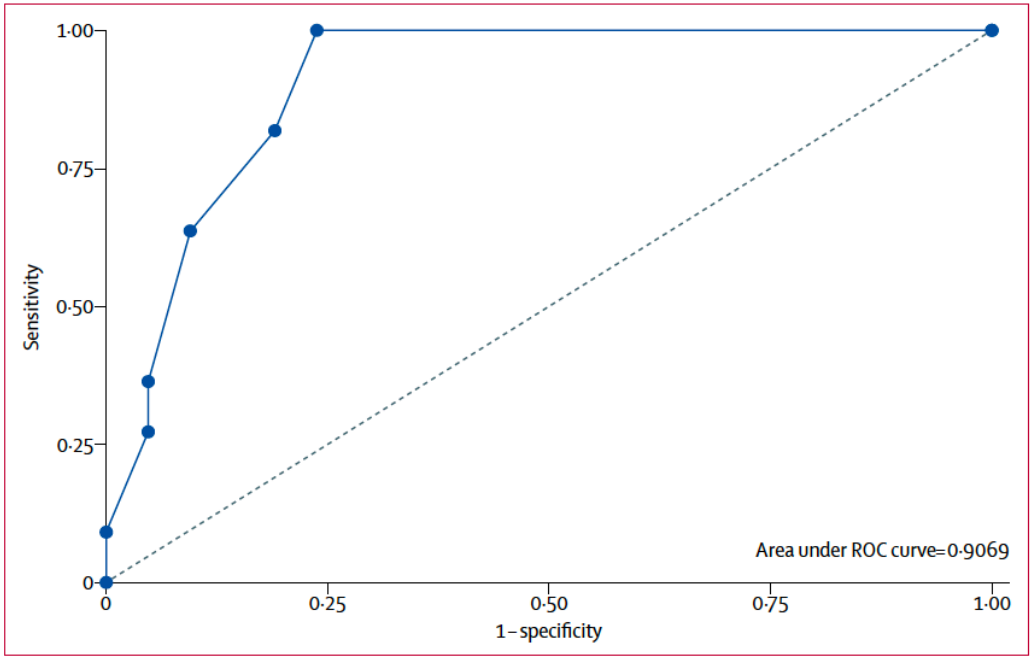


***Figure 5*: ROC curve showing predictive ability of a logistic regression analysis**
Analysis uses the persistently low versus persistently high trajectory as the outcome (or predicted) measure with the following covariates: (1) recurrent wheeze with severe exacerbations by age 3 years, (2) at least one positive skin test by age 3 years, and (3) environmental tobacco smoke exposure by age 3 years. ROC=receiver operating characteristic.

İlk 3 yaşda

1. Tekrarlayan vizing, ağır ataklar eşliğinde
2. En az 1 deri testi pozitifliği
3. Pasif sigara maruziyeti

Persistan düşük SFT

N=613	Mean(SD) % (N)
Age at follow-up (years)	9 (3.0)
Sex (male)	64% (392/613)
BMI	18.4 (3.6)
Age of asthma onset (years)	5 (3.4)
Family history of asthma (yes)	30% (184/613)
Exposure to tobacco smoke (yes)	39% (240/613)
Skin prick test positivity	59% (361/613)
FEV_1% predicted	87 (14.3)
FVC% predicted	96 (15.1)
FEV_1/FVC (%)	86 (7.0)
Bronchodilator Reversibility (%)	17.1 (12.9)
Total IgE(kU/L)	228 (458)
Blood eosinophil (%)	4.4 (3.5)
Asthma Severity	
Mild	78% (476/613)
Moderate	20% (126/613)
Severe	2% (11/613)

Clin Exp Allergy. 2018 Jan;48(1):39-47

Clinical features of the phenotypes

Feature/domain	Cluster 1 (n=132) *"Difficult asthma"*	Cluster 2 (n=210) *"Early-onset mild atopic asthma"*	Cluster 3 (n=153) *"Early-onset mild non-atopic asthma"*	Cluster 4 (n=105) *"Late-onset asthma"*	Cluster 5 (n=13) *"Exacerbation-prone asthma"*
Age of onset (years)	4.9 (2.3-7)	4.4 (3-6)	3.8 (2-6)	10.7 (9-12)	4.1 (2-5)
Asthma attacks Number, previous year	1.0 (0-1)	0.8 (0-1)	0.9 (0-1)	0.4 (0-1)	3.5 (0-7)
Allergic sensitization Sensitized	77/132 (58%)	183/210 (87%)	27/153 (18%)	67/105 (64%)	7/13 (54%)
Asthma severity					
Mild	46/132 (35%)	190/210 (90%)	141/153 (92%)	91/105 (87%)	8/13 (62%)
Moderate/severe	86/132(65%)	20/210 (10%)	12/153 (8%)	14/105 (13%)	5/13 (38%)
Cluster stability	**1.00**	**0.99**	**0.99**	**1.00**	**1.00**

Clin Exp Allergy. 2018 Jan;48(1):39-47

		Cluster 3 (n=153) *"Early-onset mild non-atopic asthma"*	Cluster 1 (n=132) *"Difficult asthma"*		Cluster 2 (n=210) *"Early-onset mild atopic asthma"*		Cluster 4 (n=105) *"Late-onset asthma"*		Cluster 5 (n=13) *"Exacerbation-prone asthma"*	
FEV_1 % predicted	Mean (95%CI)	88.4 (86-91)	83.0 (74-91)		88.0 (80-96)		87.9 (78-97)		83.2 (74-90)	
	RR (95% CI)	N/A (Reference group)	0.68 (0.53-0.86)	P<0.001	0.97 (0.79-1.20)	P=0.82	0.85 (0.75-1.25)	P=0.81	0.82 (0.39-1.22)	P=0.19
FEV_1/FVC (%)	Mean (95%CI)	86.6 (85.5-87.7)	84.8 (83.5-86.1)		86.3 (85.4-87.2)		85.4 (84.1-86.8)		83.7 (78.8-88.5)	
	RR (95% CI)	N/A (Reference group)	0.77 (0.61-1.09)	P=0.03	0.95 (0.77-1.18)	P=0.65	0.83 (0.65-1.08)	P=0.17	0.67 (0.39-1.14)	P=0.14
Bronchodilator reversibility (BDR), %	Mean (95%CI)	16.5 (14.7-18.4)	18.9 (17.6-20.2)		16.6 (14.8-18.4)		17.5 (14.6-20.5)		12.5 (9.4-15.6)	
	RR (95% CI)	N/A (Reference group)	1.18 (0.93-1.49)	P=0.16	1.00 (0.79-1.36)	P=0.98	1.08 (0.83-1.39)	P=0.55	0.58 (0.25-1.37)	P=0.22
Blood eosinophils, %	Mean (95%CI)	3.2 (2.8-3.7)	4.4 (1.8-5.65)		5.1 (2.4-7.1)		4.9 (2.5-6.6)		4.2 (1.9-4.7)	
	RR (95% CI)	N/A (Reference group)	1.62 (1.20-2.17)	P=0.001	1.94 (1.48-2.54)	P<0.001	1.88 (1.40-2.54)	P<0.001	1.51 (0.79-2.87)	P=0.20
Exposure to tobacco smoke	Frequency (%)	57/153 (37%)	62/132 (47%)		75/210 (36%)		41/105 (39%)		5/13 (38%)	
	RR (95% CI)	N/A (Reference group)	1.49 (0.93-2.39)	P=0.09	0.93 (0.61-1.44)	P=0.76	1.08 (0.65-1.79)	P=0.77	1.05 (0.32-3.37)	P=0.93
Pet ownership	Frequency (%)	10/153 (7%)	10/132 (8%)		15/210 (7%)		15/105 (14%)		1/13 (8%)	
	RR (95% CI)	N/A (Reference group)	1.06 (0.43-2.58)	P=0.90	0.99 (0.44-2.23)	P=0.99	2.15 (0.95-4.89)	P=0.07	0.006 (0.0001-2278)	P=0.68

Cluster analizi

- Cluster 1: Difficult asthma; PFT ↓, Eos ↑,
- Cluster 2: Early onset mild atopic asthma; Eos ↑, Family his of asthma↑, rhinitis ↑
- *Cluster 3: Early onset mild non-atopic asthma*
- Cluster 4: Late-onset asthma; Eos ↑,
- Cluster 5 Exacerbation-prone asthma

Clinical features of the phenotypes

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Moderate/severe	86/132(65%)	20/210 (10%)	12/153 (8%)	14/105 (13%)	5/13 (38%)
Cluster stability	**1.00**	**0.99**	**0.99**	**1.00**	**1.00**

Her fenotipte orta-ağır astımlı var: %8 ile %65 arasında değişiyor.
Difficult asthma grubunda en yüksek oranda (%65) orta-ağır astımlı

Clin Exp Allergy. 2018 Jan;48(1):39-47

Çocukluk çağı astımı için önemli belirteçler

- Başlangıç yaşı
- Allerjik sensitizasyon
- Şiddet
- Son 1 yıldaki alevlenmeler

Clin Exp Allergy. 2018 Jan;48(1):39-47

- SARP ve Trousseau Asthma Program (TAP) çalışmalarında da cluster analizlerinde tek başına ağır astım fenotipi yok. Her fenotipin içinde değişik oranlarda ağır astımlı var.

SARP: Fitzpatrick AM, Teague WG, Meyers DA, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011;127:382-389 e1-13.

TAP: Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. Eur Respir J. 2012;40:55-60.

J ALLERGY CLIN IMMUNOL
FEBRUARY 2018

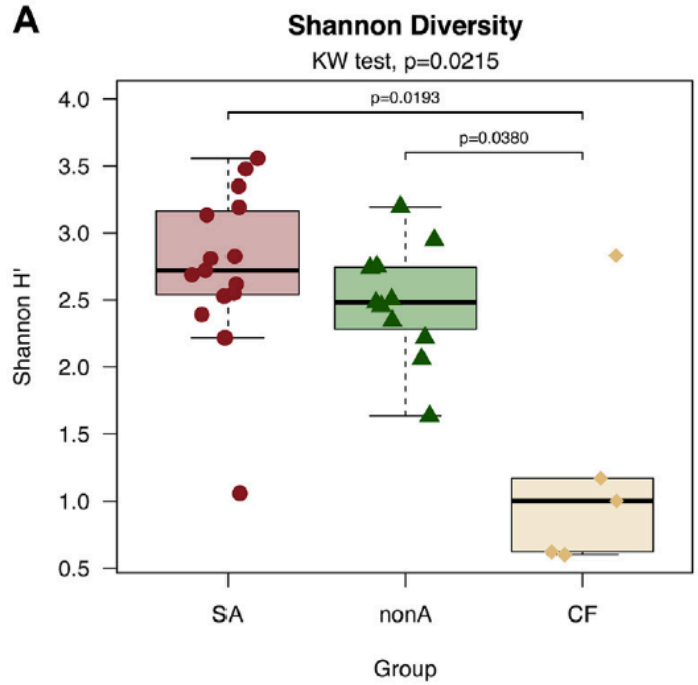
Lower airway microbiota and mycobiota in children with severe asthma

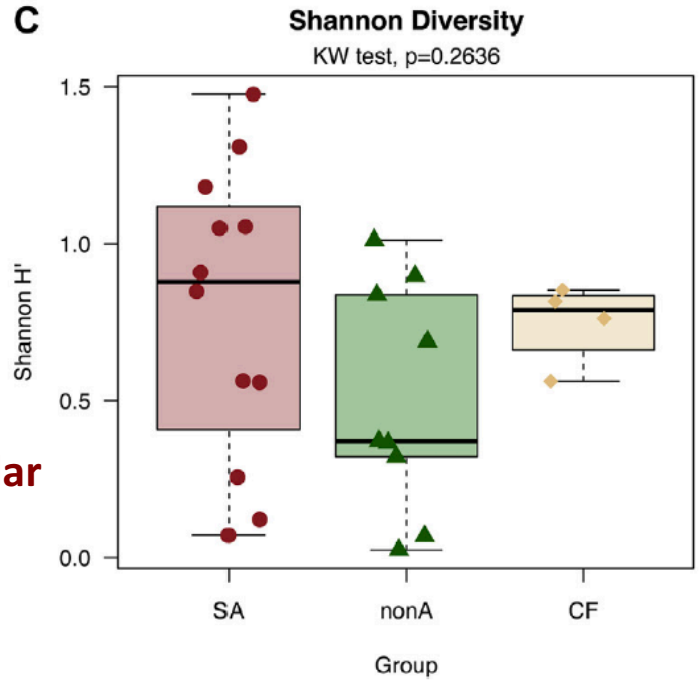
To the Editor:

Severe asthma (SA) accounts for only 5% to 10% of asthma cases, yet it remains responsible for approximately 50% of asthma-associated health care costs and a significant

TABLE I. Epidemiological and clinical characteristics of children

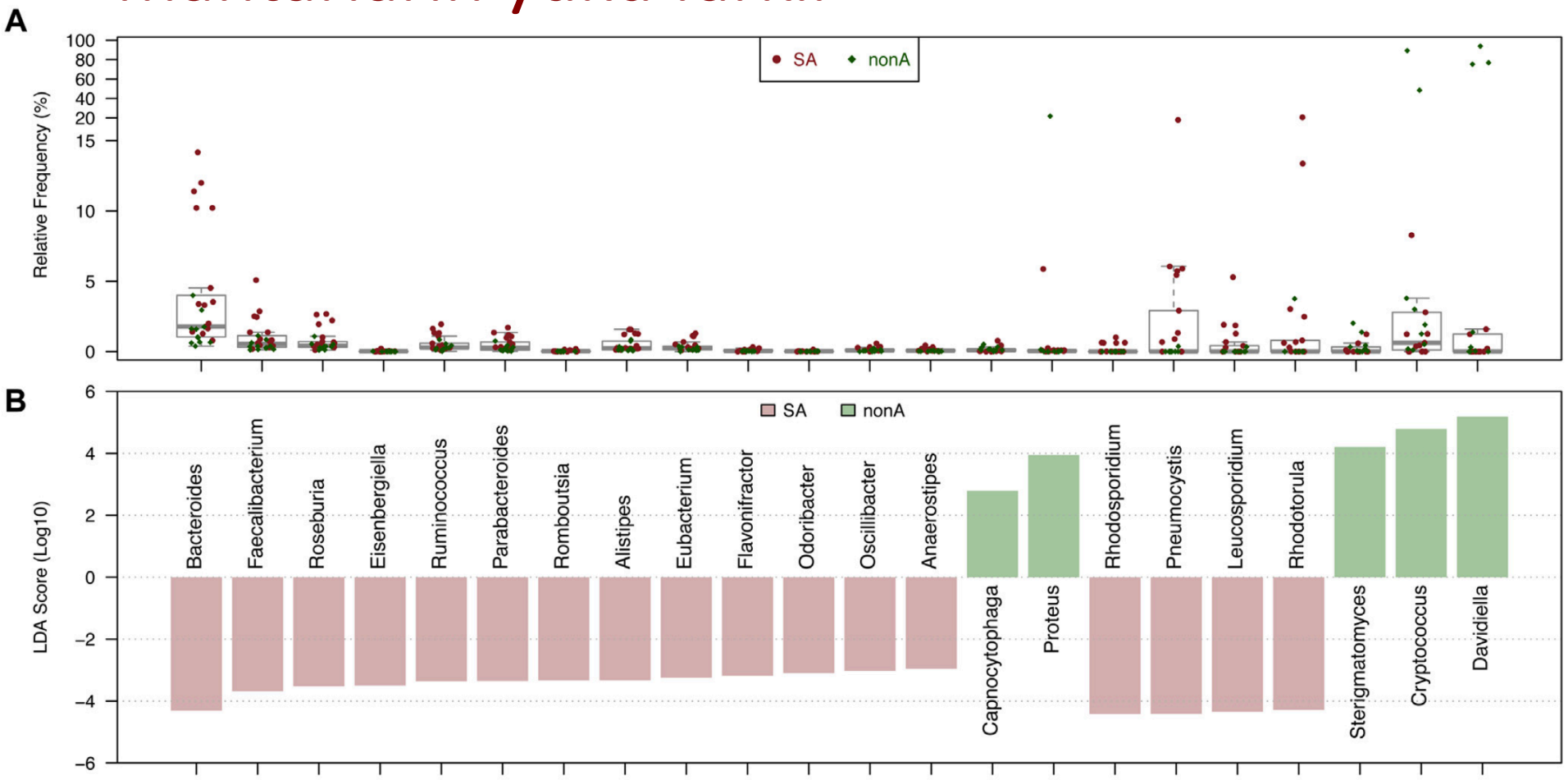
Characteristic	SA (n = 15)	non-A (n = 11)	CF (n = 5)	*P* value
Age (y)*				.0003
Mean ± SD	11.1 ± 4.5	5.2 ± 4.1	14.4 ± 2.7	
Sex				
Male	11 (73.3)	6 (54.6)	3 (60)	.6060†
Fungal culture positive	1 (6.7)	0 (0)	1 (20)	.4194†
Bacterial culture positive	3 (20)	3 (27.3)	4 (80)	.0589†
BAL EOS > 1.19 %	6 (42.9)‡	2 (18.2)	1 (20)	.4340†
BAL PMN > 3.5 %	6 (42.9)‡	9 (81.8)	5 (100)	.0401†





Bakteri ve mantar çeşitliliği ağır astım ile astımı olmayanlar arasında benzer

Alt solunum yollarında bazı bakteri ve mantarların yükü farklı



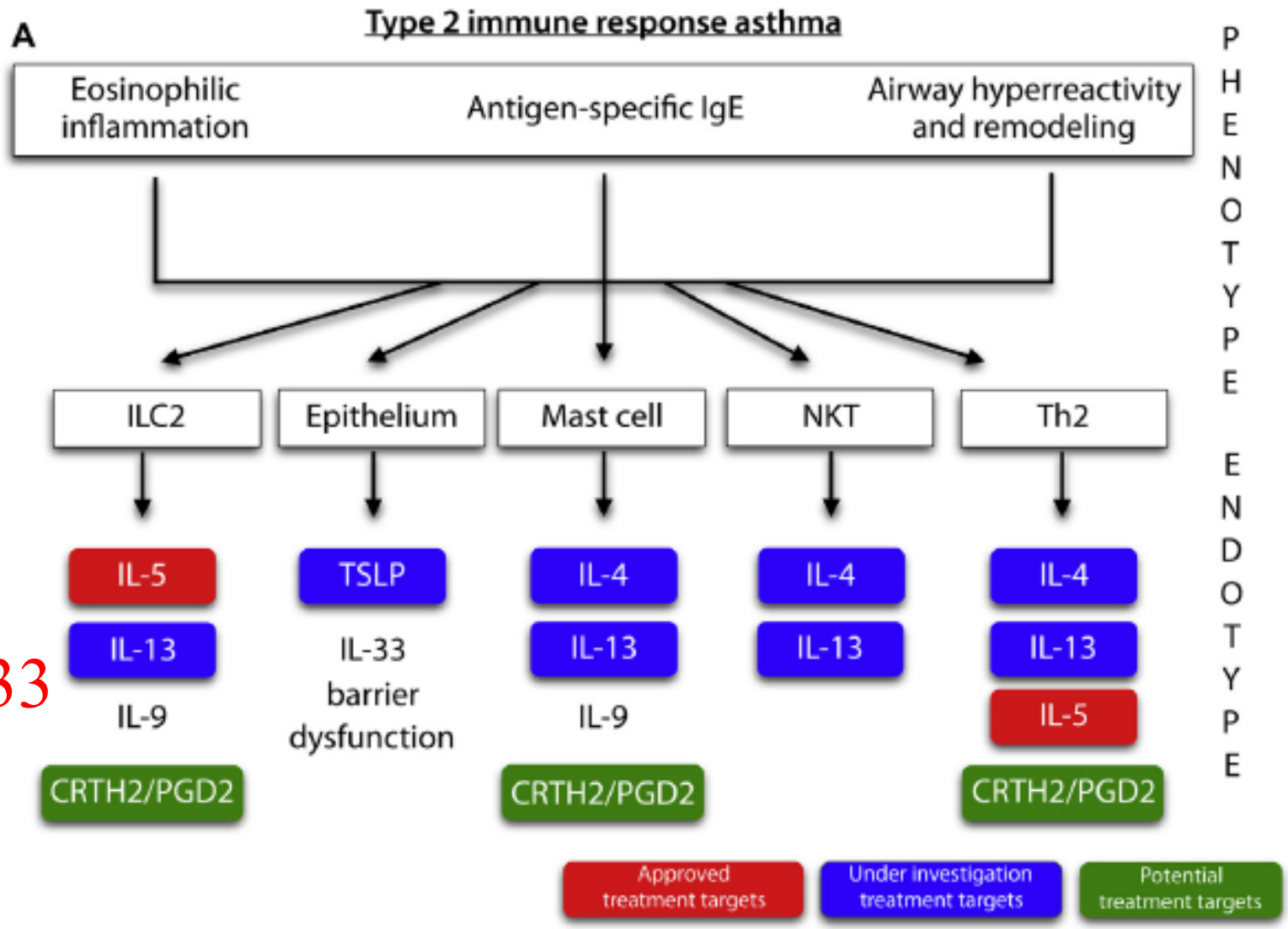
Alternaria ve Aspergillus farklı değil
Pneumocystis BAL eos sayısı ile ilişkili

JACI 2018; 141:94-103.

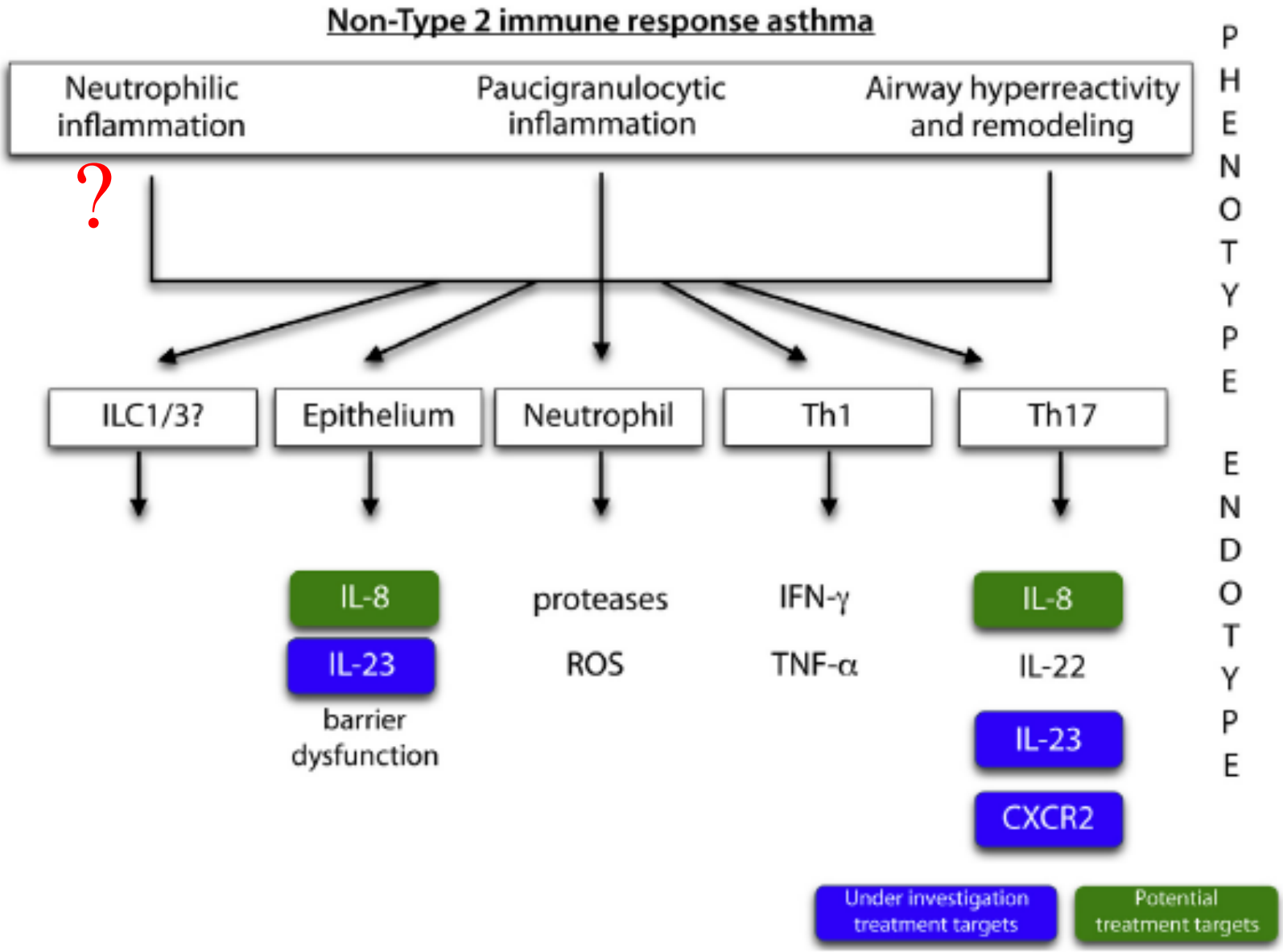
Çocuklarda ağır astım

- Solunum fonksiyon testleri
  - Bozuk
  - Normale yakın
- Eozinofili
  - Th2 (IL-4, IL-5, IL-13 artmış)
  - non Th2
- Düşük IL-10
- Artmış IL-33
- İyi prognostik faktörler
  - Havayolu intraepitelyal nötrofili
  - Artmış IL-17R ifadesi

J Allergy Clin Immunol 2013: 132:676–685.
Thorax 2014: 69:508–515.
J Allergy Clin Immunol 2012: 129:974–982



Practall Consensus Report JACI 2016;137:1347-1358



Practall Consensus Report JACI 2016;137:1347-1358

Original Article

Neutrophilic Steroid-Refractory Recurrent Wheeze and Eosinophilic Steroid-Refractory Asthma in Children

Tamazoust Guiddir, MD[a,b], Philippe Saint-Pierre, PhD[c], Elsa Purenne-Denis, MD[a], Nathalie Lambert, MD[a,b], Yacine Laoudi, MD[a], Rémy Couderc, PhD, PharmD[d], Rahelé Gouvis-Echraghi, MD[a], Flore Amat, MD[a,b], and Jocelyne Just, MD, PhD[a,b] *Paris and Toulouse, France*

What is already known about this topic? In preschool children, recurrent wheezes have a good prognosis but severe phenotypes exist. At school age, severe asthma is often associated with multiple allergies. In these 2 cases, the physiopathological pathways are not well known.

What does this article add to our knowledge? Inflammatory cells and different triggers are associated with 2 phenotypes of severe obstructive diseases during childhood: neutrophils and bacterial infection in preschool children and eosinophils and multiple allergies at school age.

How does this study impact current management guidelines? These 2 severe childhood obstructive diseases—neutrophilic steroid-refractory recurrent wheeze and eosinophilic steroid-refractory asthma—could be treated by targeted therapies such as antibiotic and T helper lymphocyte type 2 biotherapy directed towards neutrophil and eosinophil inflammation, respectively.

J Allergy Clin Immunol Pract 2017;5:1351-61

Severe Asthma Molecular Phenotype Cohort

- Orta-ağır şiddette tekrarlayan vizingli çocuklar ve
- Orta-ağır şiddette astımlı çocuklar

- Kan ve BAL hücre analizi
- Steroid yanıtı

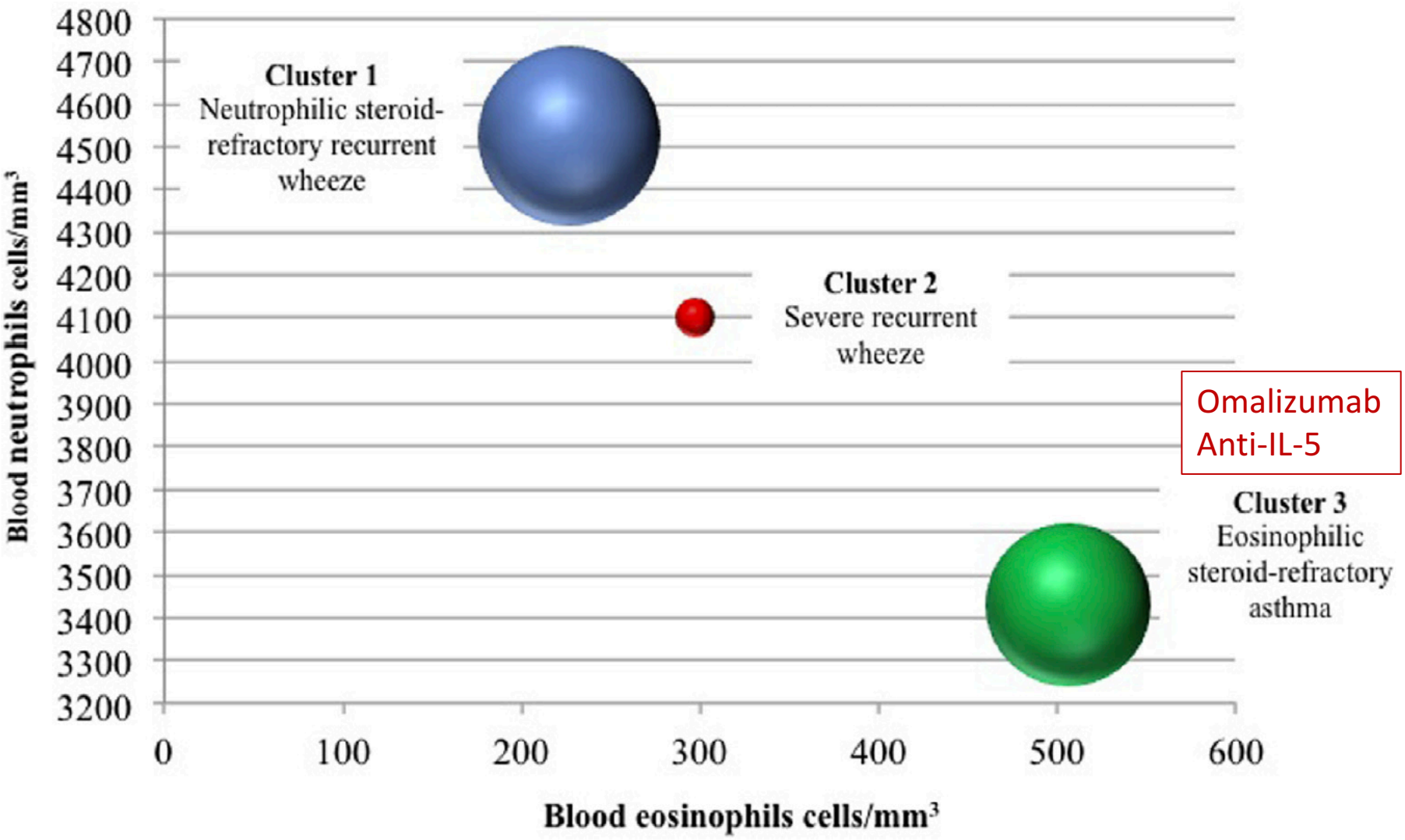
- Cluster analizi 350 çocukta (1-15 yaş) 34 farklı değişken ile yapılıyor.

J Allergy Clin Immunol Pract 2017;5:1351-61

3 cluster tanımlanıyor

Cluster 1: Neutrophilic steroid-refractory recurrent wheeze phenotype	**Cluster 2, Severe recurrent wheeze with sensitization to a single aeroallergen**	**Cluster 3, Eosinophilic steroid-refractory asthma phenotype**
N=138	N=104	N=108
uncontrolled despite high-dose inhaled corticosteroids (ICS) (92%)	controlled with high-dose ICS (63%)	uncontrolled despite high-dose ICS (76%,
history of pneumonia (31%)		allergic rhinitis, atopic dermatitis, and food allergies (82%, 40%, 31%, P < .001, respectively
gastroesophageal reflux disease (37%,		
highest blood neutrophil count (mean 4.524 cells/mm3)		higher blood eosinophil count and a higher percentage of BAL eos (506/mm3, 2.6%)
BAL bacterial culture (26%)		
Ağır astım/vizing: %94	Ağır astım/vizing: %64	Ağır astım/vizing: %86

Makrolid
GÖR tedavisi



Omalizumab
Anti-IL-5

J Allergy Clin Immunol Pract 2017;5:1351-61

Sonuç

- Ağır astım her fenotip ve endotip içinde farklı oranlarda yer alıyor:
- Sıklıkla daha atopik, eozinofili daha sık,SFT hafif düşük, reversibilite yanıtı yüksek (>%12), obezite ile ilişkisi az
- Çocuklukda ağır astım heterojen:Her fenotipin aşırı uçlarında ağır astım olguları var.
- Fenotip ve endotip tanımlamaları ağır astım öngörüsünde çok başarılı değil ama bireysel tedavi seçiminde yol gösterici